The Alkaloids—Volume 1

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The Alkaloids

Volume 1

A Review of the Literature Published between January 1969 and June 1970

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Foreword

This volume is the first in the series of annual Specialist Periodical Reports devoted to the chemistry of the Alkaloids. In preparing this first volume our aim has been not simply to record progress during a selected period, but also to include whatever background material and earlier references are necessary to enable the new work to be placed in perspective in its own particular area; in consequence we hope that the reader, whether the alkaloid specialist or the general reader, will be able to read and benefit from the discussions presented here with the minimum of reference to the standard monographs on the subject.

The alkaloid literature has been reviewed up to the end of June 1970, but for convenience most authors have started their literature surveys from January 1969; this inaugural volume, therefore, properly represents a summary of developments in the subject during an eighteen-month period. The whole field of alkaloid chemistry has been reviewed with the exception of the steroidal alkaloids of the *Solanum* and *Veratrum* groups. It has not proved possible owing to limitations of space to include these sub-groups in the present volume, and it is therefore planned to include a review of developments in this area during a two-year period in the second volume.

Although the Specialist Reports will normally consist of comprehensive annual reviews of alkaloid chemistry, we have included in this volume three chapters which, in view of their scope and character, are of a different type. The first of these is an authoritative statement on the biosynthesis of the terpenoid indole alkaloids, the main features of which are now reasonably well understood. It also seemed a most propitious moment in which to review the fascinating group of bisindole alkaloids and it will, I think, be generally agreed that the inclusion here of a definitive review by Professor Schmid and his Zürich colleagues fills a major gap in the alkaloid literature. The third non-recurrent review is by Dr. Schlittler, who has contributed a survey on the applications of alkaloids in the fields of pharmacology and clinical medicine during the last fifteen years, *i.e.* during the 'post-reserpine' period. In these Reports the pharmacology of the alkaloids will not normally be discussed, but it is appropriate to remember that the actual or reputed physiological activities of plant extracts and their widespread use in folk medicine have frequently provided the stimulus for the initial chemical investigations; and while the fascinating chemistry subsequently

revealed has proved sufficient intellectual reward to the academician, the occasional discovery of substances of clinical value has provided a welcome bonus.

This volume is the result of a cordial and enthusiastic collaboration between a team of alkaloid specialists in which I have done little more than plan the volume, plead for assistance, co-ordinate the final results, and exercise general editorial supervision. It is appropriate, therefore, that I should record here my gratitude to my collaborators for their eager participation and for the efforts they made to ensure the prompt submission of their contributions.

Aside from the deliberate omission of part of the steroid field it is likely that there will also be inadvertent omission of some minor sub-groups of alkaloids, or of material from comparatively inaccessible journals. I shall be pleased to receive information concerning any such omissions, and constructive criticisms or suggestions concerning the preparation of future Reports will also be welcomed.

J. E. SAXTON

Contents

1

Biosynthesis—I. General

BY R. B. HERBERT

This review covers the biosynthesis of alkaloids other than those derived from tryptophan and a C_9 or C_{10} terpenoid unit, which are surveyed in the succeeding chapter.

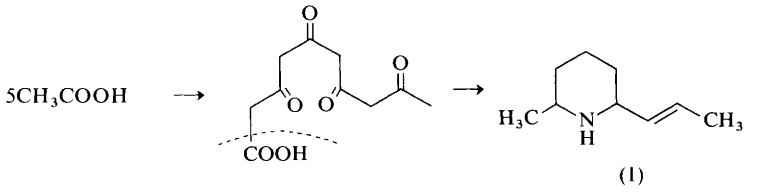
Attention is drawn to reviews which include or are concerned wholly with biosynthesis: Menispermaceae alkaloids,[1] morphine alkaloids,[2] and one which surveys the role of anthranilic acid in the biosynthesis of many alkaloid types.[3] An excellent book on alkaloid biosynthesis edited by Mothes and Schütte has appeared during 1969.[4]

Pinidine and Coniine.—Pinidine (1) is found in various species of pine, including *Pinus jeffreyi*. Inspection would indicate an origin similar to coniine (2) or to *N*-methylpelletierine (13). Whilst the former is biosynthesised by the linear combination of four acetate units,[5] the piperidine ring of the latter is generated from lysine and the side chain from acetate.[6]

The pinidine isolated after feeding [1-^{14}C]acetate to *P. jeffreyi* was degraded to reveal essentially all the activity located at the four positions expected of a linear combination of five acetate units (Scheme 1).[7] On the other hand, a low incorporation of [2-^{14}C]-DL-lysine was obtained, which partial degradation showed was not specific to the piperidine ring of the alkaloid. The incorporation found was rationalised as being the result of catabolism of the lysine to acetate. Thus, the biosynthetic pathway to pinidine is similar to that of the hemlock alkaloid coniine.

The biosynthetic sequence which leads to coniine has been further studied by two different methods. One[8] has involved the use of $^{14}CO_2$ and the other serendipity.[9] As a preliminary to tracer experiments with 5-keto-octanoic acid,

[1] C. W. Thornber, *Phytochemistry*, 1970, **9**, 157.
[2] G. Blaschke, *Mitt. deut. pharm. Ges. D.D.R.*, 1969, **39**, 225. Published in *Arch. Pharm.*, 1969, **302**, 10.
[3] D. Gröger, *Lloydia*, 1969, **32**, 221.
[4] K. Mothes and H. R. Schütte, 'Biosynthese der Alkaloide,' VEB Deutscher Verlag der Wissenschaften, Berlin, 1969.
[5] E. Leete, *J. Amer. Chem. Soc.*, 1963, **85**, 3523; 1964, **86**, 2509.
[6] R. N. Gupta and I. D. Spenser, *Phytochemistry*, 1969, **8**, 1937.
[7] E. Leete and K. N. Juneau, *J. Amer. Chem. Soc.*, 1969, **91**, 5614.
[8] S. M. C. Dietrich and R. O. Martin, *Biochemistry*, 1969, **8**, 4163.
[9] E. Leete, *J. Amer. Chem. Soc.*, 1970, **92**, 3835.



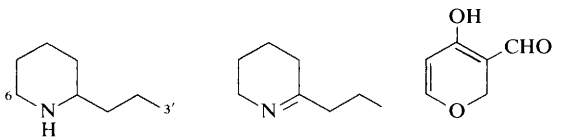
(1)

Scheme 1

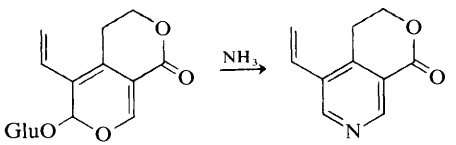
sodium [1-^{14}C]octanoate was administered to hemlock (*Conium maculatum*).[9] The coniine (2) isolated after 24 hours was found, unexpectedly, to be highly radioactive (0.45% incorporation). Further, degradation established that almost all the activity was confined to C-6; a little scrambling of the label was apparent after a feeding extending over 7 days. [8-^{14}C]Octanoate was also specifically incorporated (at the 3′ position) but here the scrambling was more pronounced. Nevertheless, the results clearly indicate a specific and intact incorporation of octanoic acid into coniine, presumably *via* 5-keto-octanoic acid.

The validity of the reported[10] incorporation of Δ^1-piperideine and its 2-carboxy-derivative into γ-coniceine (3), which is clearly in conflict with an acetate derivation for coniine, must be further doubted as incorporation of Δ^1-piperideine in hemlock could not be repeated,[9] nor was any trace of this compound found during $^{14}CO_2$ experiments.[8]

Earlier results with $^{14}CO_2$ in hemlock have been refined and a primary rôle for γ-coniceine in the formation of the other *Conium* alkaloids seems clear.[8] A biosynthetic sequence from γ-coniceine (3) → coniine (2) → *N*-methylconiine is consistent with the findings.



(2) (3) (4)



(5) (6)

An interesting non-nitrogenous base was discovered during these experiments on *Conium maculatum*. It was also isolated from *Sedum sarmentosum* and *Punica*

[10] B. T. Cromwell and M. F. Roberts, *Phytochemistry*, 1964, **3**, 369; B. T. Cromwell in 'Biosynthetic Pathways in Higher Plants,' ed. J. B. Pridham and T. Swain, Academic Press, New York, 1965, pp. 147–157.

granatum and its structure has been assigned as 3-formyl-4-hydroxy-2*H*-pyran (4).[11] This pyran was rapidly labelled during the $^{14}CO_2$ experiments in *C. maculatum* and its disappearance coincided with the appearance of alkaloids. This suggested a possible rôle for (4) in the biosynthesis of hemlock alkaloids. In addition, attention was drawn to the structural similarity of (4) to various piperidine and pyridine alkaloids, not least of which is nicotine; also the ease of amination of pyrones and the conversion of gentiopicrin (5) into gentianine (6).[12]

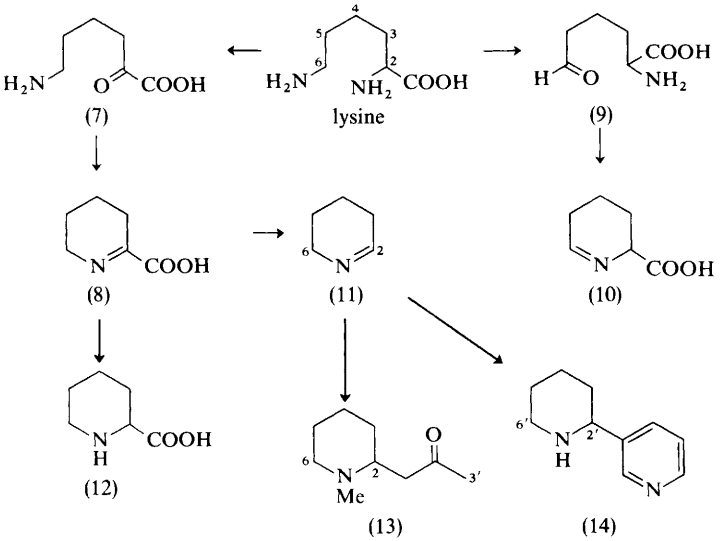
***Nicotiana* Alkaloids.**—Experiments with $^{14}CO_2$ have also been used in consideration of the origin of the pyridine ring of nicotine (27)[13] and correlated with similar work on the pyrrolidine ring of this alkaloid.[14] When *Nicotiana glutinosa* or *N. rustica* were grown in an atmosphere of $^{14}CO_2$, the greatest incorporation of $^{14}CO_2$ into the pyridine ring occurred at positions 4, 5, and 6, which were labelled to a similar extent; the incorporation at position 2 was much smaller, and similar to that at position 3. The results are in agreement with the derivation of this ring from glyceraldehyde (C_3) and aspartic acid (C_2).[15] The modes of formation of both of these precursors would lead to an equal incorporation of $^{14}CO_2$ into all the carbon atoms of each unit. The difference in activity between the two units is a measure of different dilution or incorporation rates or both.

[6-^{14}C]-Δ^1-Piperideine has been shown to be a precursor of anabasine (14) in *Nicotiana glauca*.[16] The incorporation (1.2%) was significantly higher than from cadaverine or lysine with *N. glauca* growing under similar conditions. Degradation established the presence of the label at C-6′, with C-2′, in particular, being inactive. Pelletierine (15), produced by condensation of [6-^{14}C]-Δ^1-piperideine with ethyl acetoacetate in the laboratory, was labelled solely at C-6, indicating that the 1,2-double bond is not capable of tautomeric shift to the 1,6-position.

As both lysine and Δ^1-piperideine lead to unequal labelling of C-2′ and C-6′ in anabasine, and the biosynthetic sequence must be lysine $\rightarrow$ Δ^1-piperideine (11) $\rightarrow$ anabasine (14), any other precursors for (14) after lysine must be unsymmetrical in nature. Thus cadaverine, although incorporated into anabasine, cannot be a true precursor for the alkaloid.[16] Two other groups of workers[6,8] have also cast doubt on the rôle of cadaverine in alkaloid biosynthesis, and it is worth remembering in general that even if a proposed precursor is specifically incorporated it may not lie on the normal pathway to a particular alkaloid. Rather, it may merely test the adaptability of the plant in the face of an unusual substrate.

The available results, which indicate a biosynthetic pathway to anabasine (14) similar to that to *N*-methylpelletierine, are illustrated (Scheme 2).

[11] O. A. Koleoso, S. M. Dietrich, and R. O. Martin, *Biochemistry*, 1969, **8**, 4172.
[12] H. G. Floss, U. Mothes, and A. Rettig, *Z. Naturforsch.*, 1964, **19b**, 1106.
[13] H. R. Zielke, C. M. Reinke, and R. U. Byerrum, *J. Biol. Chem.*, 1969, **244**, 95.
[14] H. R. Zielke, R. U. Byerrum, R. M. O'Neal, L. C. Burns, and R. E. Koeppe, *J. Biol. Chem.*, 1968, **243**, 4757.
[15] D. Gross in 'Biosynthese der Alkaloide,' VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, pp. 243–248.
[16] E. Leete, *J. Amer. Chem. Soc.*, 1969, **91**, 1697.



Scheme 2

***N*-Methylpelletierine.**—Labelling of *N*-methylpelletierine (13) by [6-^{14}C]-DL-lysine in *Sedum sarmentosum* has been shown to be confined to C-6 and thus the piperidine ring of this alkaloid, like anabasine (14),[16] is derived from lysine by way of unsymmetrical intermediates, and cadaverine cannot be a true precursor.[6] In confirmation of the rôle of this amino-acid, [4,5-$^{3}H_2$,6-^{14}C]-DL-lysine was incorporated into *N*-methylpelletierine without alteration of the $^{3}H : {}^{14}C$ ratio. Catabolism of lysine would have resulted in complete loss of the ^{3}H at position 4.

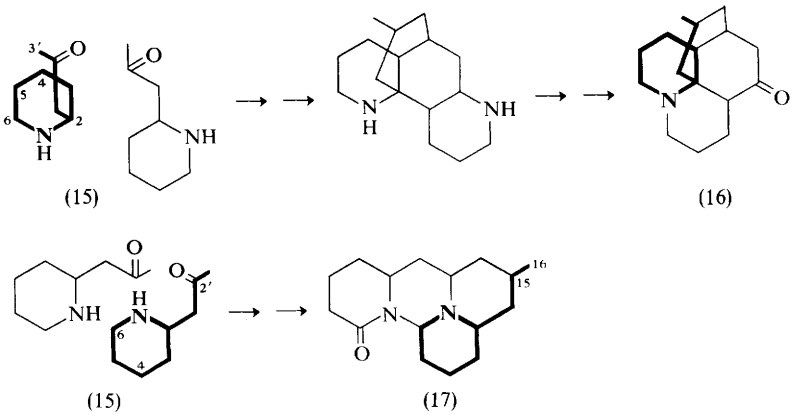
The integrity of the $^{3}H : {}^{14}C$ ratio was also maintained in the *N*-methylpelletierine and pipecolic acid (12) isolated after administration of [6-^{3}H,6-^{14}C]-DL-lysine to *S. sarmentosum*. Retention of tritium at position 6 is in agreement with retention of the ε-amino-group in lysine and loss of the α-amino-function in the formation of Δ^1-piperideine-2-carboxylic acid (8) *via* (7) rather than the reverse, which would give Δ^1-piperideine-6-carboxylic acid (10) *via* (9) with partial loss of the tritium label.

Further experiments with [6-^{3}H,6-^{14}C]-DL-lysine have been carried out on the origins of pipecolic acid (12) in *Sedum acre*, bean plants (*Phaseolus vulgaris*), a lysine-less mutant of *Neurospora crassa*, and intact rats.[17] In each case, the original $^{3}H : {}^{14}C$ ratio was maintained in the pipecolic acid isolated. This is in agreement with the conclusions from a study with ^{15}N-labelled lysine in the rat, where there was clear retention of the ε-amino-group and clear loss of the

[17] R. N. Gupta and I. D. Spenser, *J. Biol. Chem.*, 1969, **244**, 88.

α-amino-function,[18] but in contradiction with the results of a similar study in *P. vulgaris*.[19] Here, however, no clear retention or loss was apparent, and the ^{15}N content found is explained as being the result of ^{15}N enrichment of the nitrogen pool involved in transamination reactions.

The tracer results thus indicate a similar pathway to the piperidine rings of pipecolic acid (12) and *N*-methylpelletierine (13) (Scheme 2), and the latter may be derived plausibly from Δ^1-piperideine (11) by condensation with acetoacetate. The possibility that acetoacetate is a precursor is supported by the finding that the side chain of *N*-methylpelletierine is synthesized from acetate in *Punica granatum*.[20] Attempts to show the involvement of acetoacetate using [3-^{14}C]- and [4-^{14}C]-β-hydroxybutyrate, considered to be more easily manipulated than acetoacetate, were unsuccessful as the derived *N*-methylpelletierine showed a labelling pattern very similar to that found with acetate, to which presumably the β-hydroxybutyrate is first degraded.[6]



Scheme 3

***Lycopodium* Alkaloids.**—It has been suggested that lycopodine (16), cernuine (17), and related alkaloids are modified dimers of pelletierine (15) (Scheme 3).[21,23] Lysine[21] and acetate[22] serve as specific precursors of lycopodine. Further, [2-^{14}C]lysine has been specifically incorporated into cernuine (17) in *Lycopodium cernuum*.[23] The data suggest that this alkaloid, like lycopodine, is biosynthesised

[18] M. Rothstein and L. L. Miller, *J. Biol. Chem.*, 1954, **211**, 851; *J. Amer. Chem. Soc.*, 1954, **76**, 1459.
[19] H. R. Schütte and G. Seelig, *Z. Naturforsch.*, 1967, **22b**, 824.
[20] H. W. Liebisch, N. Marekov, and H. R. Schütte, *Z. Naturforsch.*, 1968, **23b**, 1116; D. G. O'Donovan and M. F. Keogh, *Tetrahedron Letters*, 1968, 265.
[21] R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, and J. T. Wrobel, *J. Amer. Chem. Soc.*, 1968, **90**, 1360.
[22] M. Castillo, R. N. Gupta, D. B. MacLean, and I. D. Spenser, unpublished results.
[23] R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *Chem. Comm.*, 1970, 409.

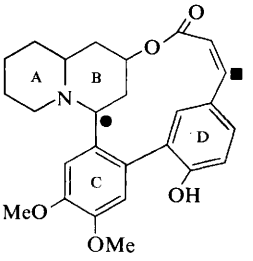
from two C_5N units derived from lysine and that incorporation is *via* a symmetrical intermediate. That pelletierine should be similarly derived from a symmetrical precursor is in contrast to the finding with *N*-methylpelletierine (see above).

Feeding experiments with labelled pelletierine (15) have been carried out on cernuine and lycopodine. [4-^{3}H,2′,6-$^{14}C_2$]Pelletierine gave radioactive cernuine (17) in *L. cernuum* without alteration of the $^3H:^{14}C$ ratio, indicating intact incorporation of pelletierine.[23] Degradation of the cernuine, however, showed twice as much activity as expected at C-15,16.

Thus, only one pelletierine unit is incorporated into cernuine and this accords with the finding on lycopodine.[24] Incorporation of [4,5-$^3H_2$,2-^{14}C]pelletierine (without change of $^3H:^{14}C$ ratio), [6-^{14}C]pelletierine, and [2,3′-$^{14}C_2$]pelletierine was obtained in *Lycopodium tristachyum*. Degradation quite clearly established that whilst pelletierine does not give one C_8 unit (normal bond thickness in 16) it is utilised intact for the other C_8 unit (heavy bonding in 16).

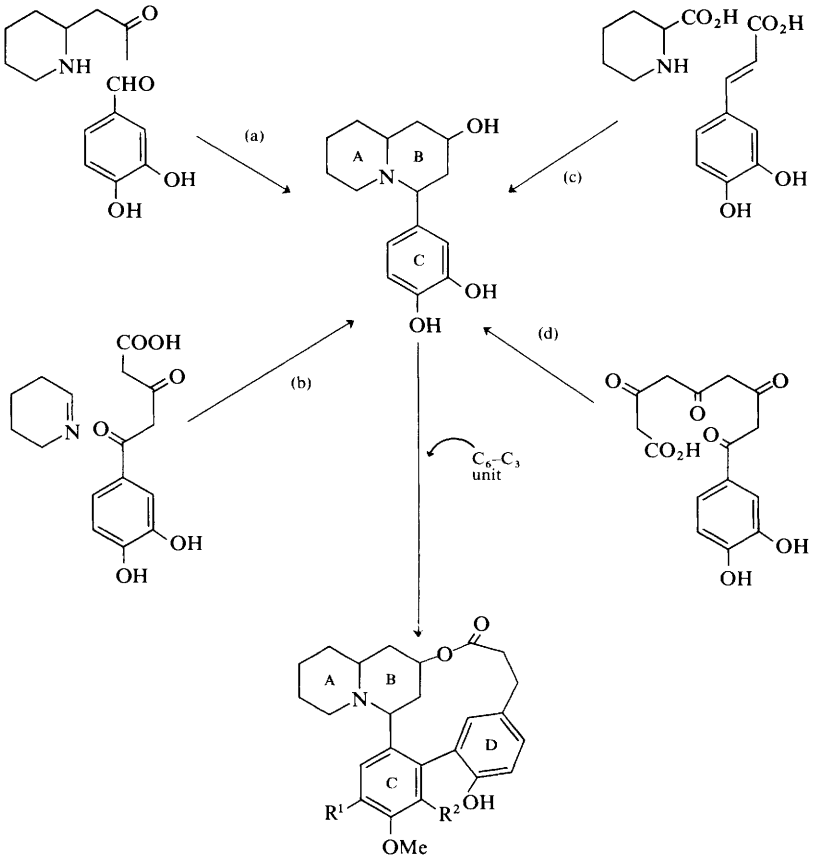
Lythraceae Alkaloids.—Cryogenine (18) has been shown to incorporate [3-^{14}C]-phenylalanine in *Heimia salicifolia*.[25] Oxidative degradation established the incorporation of labels at the positions shown in (18); the difference in incorporation of the two units may be a function of the stage at which they normally enter the biosynthetic pathway. Although ring D and the whole of its C_3 side chain are probably derived from phenylalanine, it is not yet clear whether this precursor supplies three or only one carbon atom of the quinolizidine system.

The possible origins of rings A, B, and C are illustrated for the alkaloids decodine (19) and decinine (20) (Scheme 4).[26] Both [2-^{14}C]-DL-lysine and [6-^{14}C]-DL-lysine were incorporated into these alkaloids in *Decodon verticillatus*.[26] Degradation indicated that lysine was utilized as an intact C_5N unit and, further, a symmetrical intermediate was involved. [1-^{14}C]Lysine gave totally inactive alkaloid.



(18) (● : 31%; ■ : 61%)

[24] M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, and I. D. Spenser, *J. Amer. Chem. Soc.*, 1970, **92**, 1074.
[25] A. Rother and A. E. Schwarting, *Chem. Comm.*, 1969, 1411.
[26] S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *Chem. Comm.*, 1970, 396.



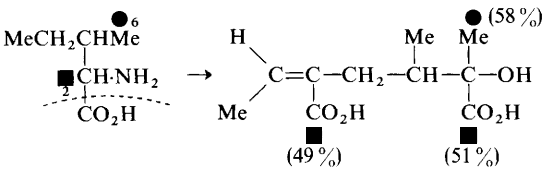
(19) R^1 = H, R^2 = OH
(20) R^1 = OMe, R^2 = H

Scheme 4

Only routes (a) and (b) are consistent with these results. It is interesting to note that if pelletierine is implicated in the biosynthesis of these alkaloids [route (a)] it should be derived from a symmetrical intermediate as is apparently true for pelletierine in the biosynthesis of lycopodine alkaloids (see above). On the other hand, Δ^1-piperideine [route (b)] is derived in an unsymmetrical way from lysine in the biosynthesis of anabasine and *N*-methylpelletierine (see above). Route (a) would, therefore, seem more likely.*

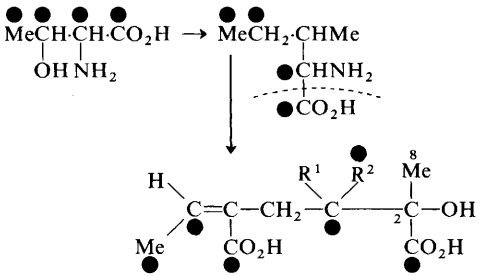
* Recent experiments with [1,2-$^{14}C_2$]phenylalanine further support route (a). S. H. Koo, F. Comer, and I. D. Spenser, *Chem. Comm.*, 1970, 897.

Pyrrolizidine Group.—Evidence from two sources indicates that the C_{10} necic acids are derived by the coupling of two units derived from isoleucine. Earlier work had indicated that the left-hand C_5 unit of seneciphyllic acid (22) is derived from isoleucine and its biological precursors threonine and aspartic acid.[27] Mevalonic acid was not incorporated but the *S*-methyl group of methionine served as a fairly specific precursor for C-8.



Scheme 5

Further experiments with threonine and isoleucine have been carried out in *Senecio magnificus*.[28] Both [2-^{14}C]- and [6-^{14}C]-isoleucine were incorporated into senecic acid (21) and degradation gave a pattern of incorporation consistent with biosynthesis from two isoleucine units (Scheme 5). [*U*-^{14}C]-L-Threonine was equally well incorporated into senecic acid, which was shown to contain essentially no activity at C-2 and C-8, consistent with the way in which threonine condenses with pyruvic acid to give isoleucine; the route from threonine to senecic acid is illustrated (Scheme 6). In these three feeding experiments the incorporation of radioactivity into the main alkaloidal component of this plant, retronecine, was very low.



(21) $R^1 = H$, $R^2 = Me$
(22) $R^1R^2 = CH_2$

Scheme 6

[27] D. H. G. Crout, M. H. Benn, H. Imaseki, and T. A. Geissman, *Phytochemistry*, 1966, **5**, 1.
[28] D. H. G. Crout, N. M. Davies, E. H. Smith, and D. Whitehouse, *Chem. Comm.*, 1970, 635.

These findings required a re-evaluation of the result which suggested that C-8 in seneciphyllic acid (22) was derived from a C_1 unit.[27] It was possible to argue that the label in [*methyl*-^{14}C]methionine might have been included, *via* the one-carbon pool, into C-3 of serine and thence into pyruvic acid and seneciphyllic acid, bearing in mind, particularly, the low overall incorporation into the parent alkaloid (seneciphyllene) and the appreciable randomisation of the label between the necic acid and the pyrrolizidine base. In support of this explanation, a specific incorporation of [*methyl*-^{14}C]-L-methionine into C-3 of serine was obtained in pea seedlings.

Tracer experiments with sodium [2-^{14}C]acetate in *Senecio sceleratus* and *S. isatidens* led independently to the same conclusion about the origin of the C_{10} necic acids: degradation indicated a common origin for both halves of retronecic and senecic acids.[29]

Tropane and Pyrrolidine Alkaloids.—The biosynthesis of cuscohygrine (29) has been examined in *Scopolia lurida* and *Atropa belladonna*. Both [1-^{14}C]acetate and [2-^{14}C]acetate were specifically incorporated into cuscohygrine in the latter plant.[30] Degradation revealed a labelling pattern in the C_3 chain [see (29)], consistent with an origin from acetoacetate.

The results with [1-^{14}C]acetate in *S. lurida* support this conclusion. Incorporations for this precursor as well as [2-^{14}C,δ-^{15}N]ornithine, [1,4-$^{14}C_2$]putrescine, and [4-^{3}H]-*N*-methylputrescine were recorded in both cuscohygrine (29) and hyoscyamine (30).[31] Degradation of the cuscohygrine in each case, which was to hygrinic acid (31), showed that the activity from these precursors (excluding acetate) was confined almost entirely to the pyrrolidine ring.

In agreement with similar experiments[32] on nicotine and hyoscyamine (*Datura metel*) *N*-methylputrescine (24) was a much better precursor for cuscohygrine and hyoscyamine in *S. lurida* than either putrescine or ornithine. [2-^{14}C,δ-^{15}N]Ornithine was incorporated into cuscohygrine with no loss of ^{15}N relative to ^{14}C, and thus the nitrogen atom in cuscohygrine arises specifically from the δ-amino-group of ornithine.[31] It was concluded from these data that decarboxylation and *N*-methylation precede cyclisation to the *N*-methylpyrrolidine ring, with δ-*N*-methylaminobutyraldehyde (25) or its cyclic form (26) as an intermediate; a similar rôle for the latter compound has been demonstrated in nicotine biosynthesis.[33]

Independent results in *Atropa belladonna* confirm that it is the δ-amino-group of ornithine which is utilized in the biosynthesis of cuscohygrine (29) and hyoscyamine (30).[34] Whilst δ-*N*-methyl-[^{3}H]ornithine serves as a good precursor for these alkaloids with a major portion of the radioactivity confined to the

[29] C. G. Gordon-Gray and F. D. Schlosser, *J. S. African Chem. Inst.*, 1970, **23**, 13.
[30] F. E. Baralle and E. G. Gros, *Phytochemistry*, 1969, **8**, 849, 853.
[31] H. W. Liebisch, A. S. Radwan, and H. R. Schütte, *Annalen*, 1969, **721**, 163.
[32] H. W. Liebisch, W. Maier, and H. R. Schütte, *Tetrahedron Letters*, 1966, 4079; H. R. Schütte, W. Maier, and K. Mothes, *Acta Biochim. Polon.*, 1966, **12**, 401.
[33] E. Leete, *J. Amer. Chem. Soc.*, 1967, **89**, 7081.
[34] F. E. Baralle and E. G. Gros, *Chem. Comm.*, 1969, 721.

N-methyl groups of the products, α-*N*-methyl-[^{3}H]ornithine showed minute non-specific incorporation.

Thus, not only is it the δ-amino-group in ornithine which is retained in these two alkaloidal types, but also the *N*-methyl group they bear can originate efficiently from δ-*N*-methylornithine (23). These results further agree with similar findings for the biosynthesis of the *N*-methylpyrrolidine ring of nicotine.[35] Results which suggest a similar sequence but utilizing the α-amino-function for the biosynthesis of nicotine and the tropane alkaloids have been reported, however.[36]

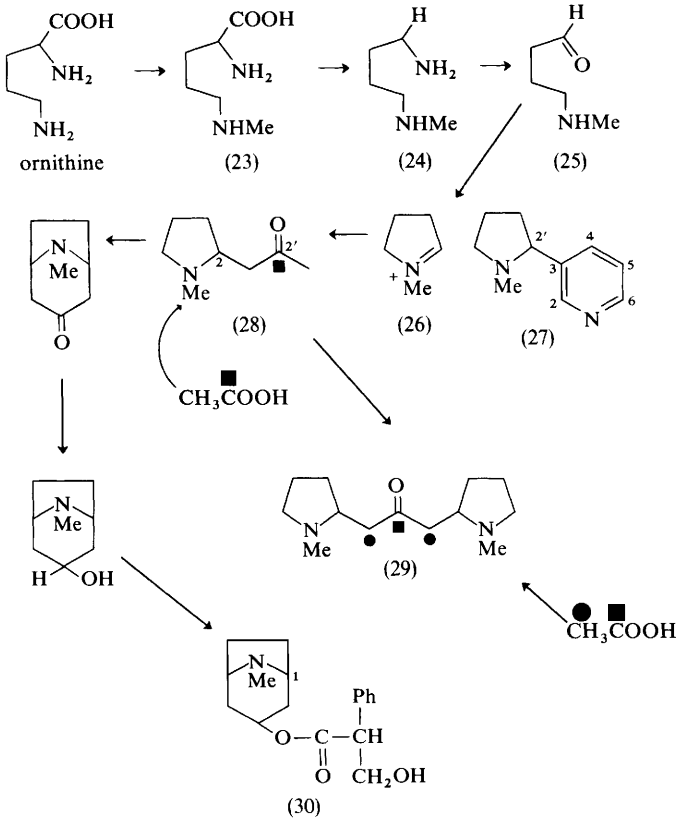
[2-^{14}C]Ornithine has been shown to be a precursor for meteloidine (32) in *Datura meteloides*.[37] Degradation established that radioactivity was confined to the bridgehead carbon atoms.

The biosynthesis of hygrine (28) and its possible rôle as a precursor for cuscohygrine (29) and the tropane alkaloids have been investigated. Both [2-^{14}C]-ornithine and [1-^{14}C]acetate were specifically incorporated into (28, the acetate labelling is indicated) in *Nicandra physaloides*.[38] The confinement of the ornithine label to C-2 is in agreement with a similar specific incorporation of this label into C-1 of hyoscyamine (30).[39]

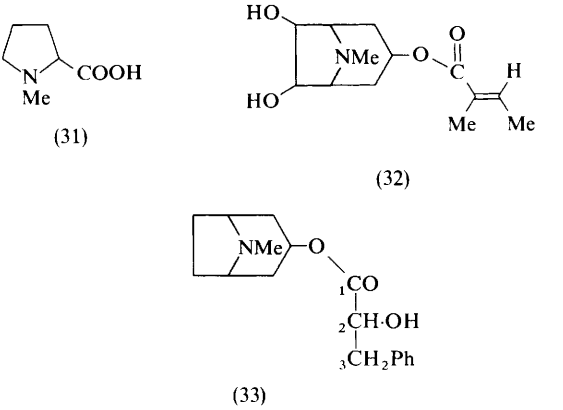
When (±)-[*N-methyl*-^{14}C,2′-^{14}C]hygrine was administered to *Datura stramonium*, a 2.1% incorporation into hyoscyamine (30) was obtained.[38] Degradation showed that the ratio between the two labels was the same as in the precursor. A similar incorporation (1.2%) into cuscohygrine (29) in *Scopolia lurida* was obtained for the doubly-labelled hygrine. As expected, the *specific* activity in the *N*-methyl groups of the cuscohygrine was one half of that required to maintain the *N*-methyl : C-2′ ratio of activities of the administered hygrine. Therefore the second pyrrolidine ring did not arise by degradation of the hygrine.

The tracer results obtained show then that hyoscyamine and cuscohygrine originate from hygrine (28). The route, ornithine ⟶ hygrine, requires in particular the accommodation of δ-*N*-methylornithine as an intermediate and incorporation of C-2 and the δ-amino-group of ornithine without loss of uniqueness. If a single route to hygrine operates, then putrescine cannot be a normal precursor because of its symmetry. If it can be assumed not to be a true precursor (*cf.* cadaverine in the biosynthesis of the piperidine ring), then a biosynthetic route to hyoscyamine (30) and cuscohygrine (29) *via* hygrine (28) can be proposed (Scheme 7)[38] which will satisfy the experimental results. The quaternary compound (26) does not apparently undergo 1,2- to 1,6-double bond tautomerism as C-2 is specifically incorporated into C-2′ of nicotine (27).[33]

[35] T. J. Gilbertson and E. Leete, *J. Amer. Chem. Soc.*, 1967, **89**, 7085; E. Leete, E. G. Gros, and T. J. Gilbertson, *Tetrahedron Letters*, 1964, 587.
[36] H. B. Schröter and D. Neumann, *Tetrahedron Letters*, 1966, 1273, 1279.
[37] E. Leete and S. J. Nelson, *Phytochemistry*, 1969, **8**, 413.
[38] D. G. O'Donovan and M. F. Keogh, *J. Chem. Soc.* (*C*), 1969, 223.
[39] E. Leete, *J. Amer. Chem. Soc.*, 1962, **84**, 55; A. A. Bothner-By, R. S. Schutz, R. F. Dawson, and M. L. Solt, *ibid.*, p. 52.


COOH
NH2
NH2
ornithine
COOH
NH2
NHMe
(23)
H
NH2
NHMe
(24)
H
O
NHMe
(25)
N
Me
O
O
2'
N
2
Me
(28)
CH3COOH
N
+
Me
(26)
2'
4
3
5
2
6
N
Me
N
(27)
N
Me
H
OH
O
N
Me
N
Me
(29)
CH3COOH
N
Me
1
Ph
O—C—CH
O
CH2OH
(30)

Scheme 7


COOH
N
Me
(31)
HO
NMe
O
O
C
H
HO
Me
Me
(32)
NMe
O
1CO
2CH·OH
3CH2Ph
(33)

The origin of the phenyl-lactic acid moiety of littorine (33) in *Datura sanguinea* has been shown to be from phenylalanine.[40] A specific incorporation of [1-^{14}C]- and [3-^{14}C]-phenylalanine was observed into carbons 1 and 3 respectively of the side chain of the phenyl-lactic acid moiety in littorine. That phenylalanine was a better precursor for littorine than for hyoscyamine (30) and hyoscine suggests perhaps that phenylalanine is a more immediate precursor of phenyl-lactic acid than of tropic acid.

Quinoline and Acridone Alkaloids.—Earlier studies have shown that the quinoline nucleus of skimmianine (38) and dictamnine (37) is derived from anthranilic acid and acetate. Whilst incorporation of mevalonate into dictamnine in *Dictamnus albus*[41] and into the furanoquinoline alkaloids of *Skimmia japonica*[42] could not be demonstrated, positive results have been obtained in *Fagara coco*.[43] [4-^{14}C]Mevalonic acid, [5-^{14}C]mevalonic acid, and [1-^{14}C]dimethylallyl alcohol were satisfactorily incorporated into skimmianine (38) and the activity was confined essentially to C-2, C-3, and C-3 respectively.

2,4-Dihydroxyquinoline (34) is known to be a precursor of kokusaginine (39).[44] When [3-^{14}C]-2,4-dihydroxyquinoline was fed to *Skimmia japonica*, incorporation into dictamnine (37) and platydesminium salt (36) was 1.3% and 2% respectively.[42] The dimethylallylquinoline (35) (specifically labelled with ^{14}C as indicated in the formula) was better incorporated (3.8 and 4.7% respectively), in accord with the biosynthetic route described below; degradation of the dictamnine from this feed showed a specific labelling of position 3 as anticipated.

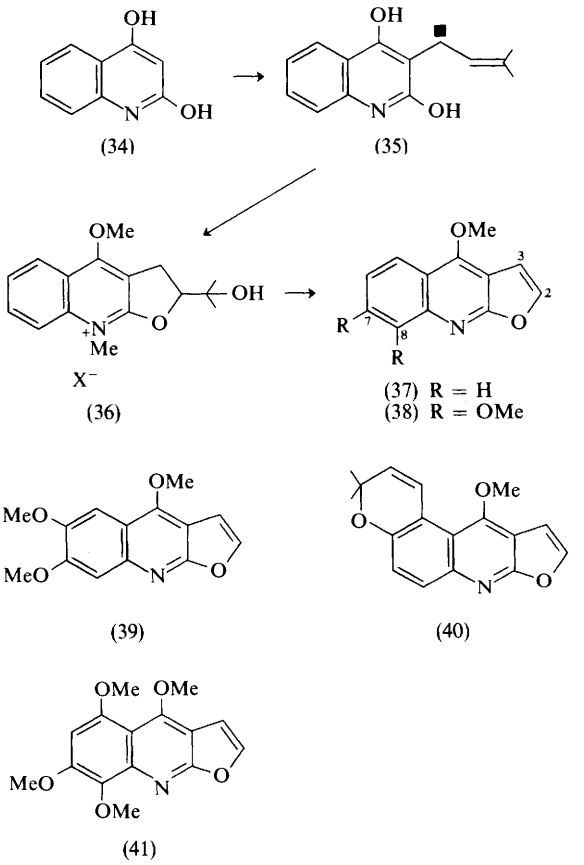
[3-^{14}C]-2,4-Dihydroxyquinoline was also incorporated efficiently into skimmianine (38) in this plant although the incorporation (0.6%) was lower than into dictamnine. Thus hydroxylation of C-7 and C-8 probably occurs at a later stage in the biosynthesis.

The above results strongly suggest that in the biological formation of the furanoquinoline alkaloids an isoprene unit (probably as isopentenyl pyrophosphate) is introduced into 2,4-dihydroxyquinoline to give (35). Cyclisation of this intermediate leads to isopropylidene-furanoquinolines *e.g.* platydesminium salt (36). Then elimination of the side chain gives the dictamnine (37) type.

When [4-^{3}H]anthranilic acid was administered to *Acronychia baueri*, skimmianine (38) and acronidine (40) showed approximately 10% and 20% tritium retention respectively when compared to the radioactivity incorporated into the acridone alkaloids of this plant.[45] These results were taken to indicate a partial 'NIH' shift on hydroxylation, in which one of the *ortho* positions was favoured over the other. However, the results for acronycidine (41) do not satisfactorily support this view; the incorporations as well as the retention of tritium in skimmianine and acronidine are low and the sites of tritium labelling were not

[40] W. C. Evans and V. A. Woolley, *Phytochemistry*, 1969, **8**, 2183.
[41] I. Monković, I. D. Spenser, and I. O. Plunkett, *Canad. J. Chem.*, 1967, **45**, 1935.
[42] J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 621.
[43] A. O. Colonna and E. G. Gros, *Chem. Comm.*, 1970, 674.
[44] M. Cobet and M. Luckner, *European J. Biochem.*, 1968, **4**, 75.
[45] C. R. Hall and R. H. Prager, *Austral. J. Chem.*, 1969, **22**, 2437.

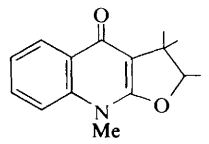
demonstrated; presumably these results will be verified, *e.g.* by using double labelling with ^{14}C and ^{3}H.



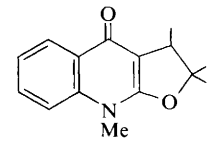
The alkaloids from *Ravenia spectabilis* and *Flindersia ifflaiana* exhibit an interesting structural variation within the quinoline group and some evidence has been presented for their genesis *via* biological Claisen rearrangements.[46] *F. ifflaiana* produces ifflaiamine (42) and (43) whilst ravenoline (44) and ravenine (45) are isolated from *R. spectabilis*. When ravenine (45) (with a ^{14}C label as indicated) was fed to *R. spectabilis*, a 0.75% incorporation into ravenoline (44) was obtained. That rearrangement to ravenoline was not taking place during work-up was proved when ravenoline was submitted to the normal isolation procedure in the presence of radioactive ravenine; the ravenoline was inactive.

[46] T. R. Chamberlain, J. F. Collins, and M. F. Grundon, *Chem. Comm.*, 1969, 1269.

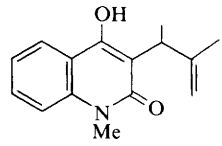
The quinoline (46) is suggested as an intermediate between (45) and (44). Ring closure of (46) and (44) would give ifflaiamine (42) and (43) respectively.



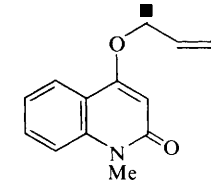
(42)



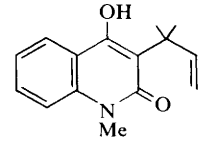
(43)



(44)



(45)

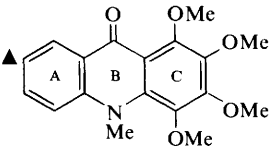


(46)

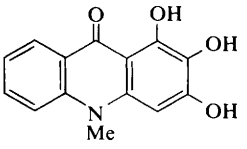
Furanoquinoline alkaloids are synthesised by *Acronychia baueri* and *Evodia xanthoxyloides*. These species are also rich in acridone alkaloids and, not unexpectedly, anthranilic acid serves as a precursor for this group of alkaloids. [5-^{3}H]Anthranilic acid gave active melicopicine (47), melicopine, and melicopidine.[47] The site of the tritium (indicated in 47) was established by bromination of melicopicine, and a specific incorporation of anthranilic acid was indicated, in agreement with similar findings for arborinine.[48]

[3-^{14}C]Tryptophan gave inactive alkaloids but tritiated 2,4-dihydroxyquinoline (34) and its *N*-methyl derivative were incorporated into (47) (0.009% and 0.020% respectively); an early route had suggested the derivation of what was essentially (34) from tryptophan. Radioisotope dilution showed the presence of both these quinoline precursors together with *N*-acetyl- and *N*-methylanthranilic acid in *A. baueri*. A satisfactory incorporation of *N*-methylanthranilic acid into (47) was found in *Evodia xanthoxyloides*, and this, together with its natural occurrence, indicates that early methylation may be important in the biosynthesis of acridone alkaloids.

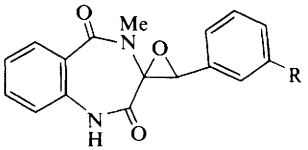
[47] R. H. Prager and H. M. Thredgold, *Austral. J. Chem.*, 1969, **22**, 2627.
[48] D. Gröger and S. Johne, *Z. Naturforsch.*, 1968, **23b**, 1072.



(47)



(48)



(49) R = H
(50) R = OH

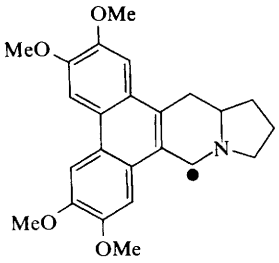
Ring C of *e.g.* (47) might plausibly be derived from acetate and incorporation of [1-^{14}C]acetate into melicopicine (47) was recorded, whilst [2-^{14}C]mevalonic acid gave inactive alkaloid. The acridone (48) was also not incorporated into (47).

Benzodiazepine Alkaloids.—Cyclopenin (49) and cyclopenol (50) are isolated from *Penicillium cyclopium*. Their biosynthesis would appear to involve one molecule of phenylalanine and one of anthranilic acid and indeed the biosynthetic pathway to viridicatin and viridicatinol in *Penicillium viridicatum* from these two amino-acids has (49) and (50) as intermediates.[49]

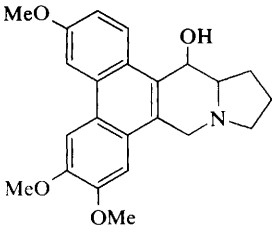
The following were administered separately to *P. cyclopium*:[50] [*carboxyl*-^{14}C]- and [^{15}N]-anthranilic acid, phenylalanine with ^{14}C labels at positions 1, 2, and 3, and also ^{15}N-labelled phenylalanine and [*methyl*-^{14}C]methionine. The results show an intact incorporation of all the atoms of phenylalanine and anthranilic acid into both (49) and (50), with L-phenylalanine preferred over the D-isomer. The *N*-methyl group originates from the *S*-methyl group of methionine. The cyclic dipeptide formed from these two amino-acids is presumably an intermediate on the pathway to the alkaloids. As phenylalanine serves as a precursor for cyclopenol, the origin of the hydroxy-group is by *meta*-hydroxylation of phenylalanine.[51] Further, *m*-tyrosine and tyrosine are only unspecific precursors.

***Tylophora* Alkaloids.**—Administration of [2-^{14}C]tyrosine to *Tylophora asthmatica* was followed by the isolation of radioactive tylophorine (51) and tylophorinine (52).[52] Degradation of the former indicated an exclusive incorporation of the label at ● in (51). It is perhaps surprising that one rather than two tyrosine units is apparently involved in the biosynthesis of tylophorine, but on the other hand the tracer experiments on these alkaloids have only just begun.

[49] M. Luckner and K. Mothes, *Arch. Pharm.*, 1963, **296**, 18; *Tetrahedron Letters*, 1962, 1035.
[50] L. Nover and M. Luckner, *European J. Biochem.*, 1969, **10**, 268.
[51] L. Nover, *Pharmazie*, 1969, **24**, 365.
[52] N. B. Mulchandani, S. S. Iyer, and L. P. Badheka, *Phytochemistry*, 1969, **8**, 1931.



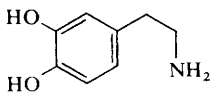
(51)



(52)

Cactus Alkaloids.—Detailed attention has been given to establishing the sequence of hydroxylation and methylation which leads from dopamine (53) to mescaline (57). The combined results from *Lophophora williamsii*[53,54,55] and *Trichocereus pachanoi*[54] establish that methylation of dopamine to (54) is a first step; neither 3-hydroxy-4-methoxyphenethylamine[53,54,55] nor the naturally occurring 3,4-dimethoxyphenethylamine[53,54] are significantly incorporated. Hydroxylation of 3-methoxy-4-hydroxyphenethylamine must be the next step but the results are not entirely satisfactory. Although 3,4-dihydroxy-5-methoxyphenethylamine (55) is well incorporated in *T. pachanoi* (31.6%), incorporation in *L. williamsii* is lower than for (54) (1.56% *vs.* 2.75%).[54] Similar low values have been recorded for 3,4,5-trihydroxyphenethylamine in this plant[54,55] but an efficient conversion to mescaline (16.3%) has been recorded in *T. pachanoi*.[54] (It may be significant that *T. pachanoi*, in contrast to *L. williamsii*, does not produce tetrahydroisoquinolines.) Finally, *O*-methylation of (55) gives 4-hydroxy-3,5-dimethoxyphenethylamine (56), the immediate precursor of mescaline.[53,54,55]

Although 3-hydroxy-4,5-dimethoxyphenethylamine is a very poor precursor of mescaline,[53,54,55] it was found to be efficiently utilised in the biosynthesis of anhalamine (58)[54,56] and anhalonidine (59)[56] in *L. williamsii*. Further, the results indicated that mescaline and these isoquinoline alkaloids share a common pathway until appropriate methylation of 3,4-dihydroxy-5-methoxyphenethylamine brings about a divergence.



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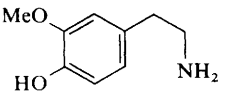

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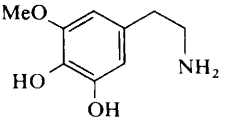
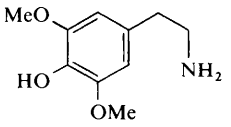
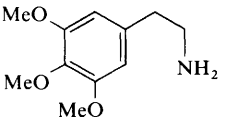


(55)

[53] A. G. Paul, H. Rosenberg, and K. L. Khanna, *Lloydia*, 1969, **32**, 36; H. Rosenberg, K. L. Khanna, M. Takido, and A. G. Paul, *ibid.*, p. 334.
[54] J. Lundström and S. Agurell, *Tetrahedron Letters*, 1969, 3371.
[55] K. L. Khanna, H. Rosenberg, and A. G. Paul, *Chem. Comm.*, 1969, 315.
[56] A. G. Paul, K. L. Khanna, H. Rosenberg, and M. Takido, *Chem. Comm.*, 1969, 838.



(56)



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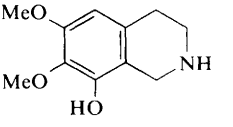

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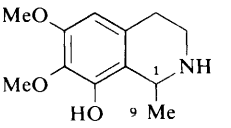

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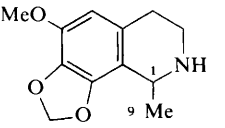
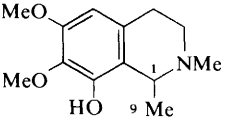
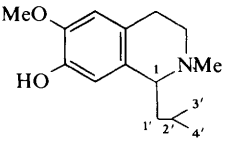


(60)



(61)



(62)

L. williamsii does not, however, use any of the above di- and tri-hydroxylated phenethylamines as efficiently as it uses dopamine in the biosynthesis of anhalonine (60)[54] and pellotine (61).[57] Indeed, the incorporation of these amines, in general, has been found to be very low. Part of the solution[56] to the incorporations found for pellotine may lie in the interconvertibility of this alkaloid and (59) in the plant, in which demethylation appears to be favoured.[57] Certainly, the biosynthesis of these simple isoquinolines is in need of further study.

The origin of the C-2 unit in anhalonidine (59) and pellotine (61) has received attention. [2-^{14}C]Acetate gave pellotine with an approximately equal distribution of the label over carbons 1 and 9, whilst [1-^{14}C]acetate labelled C-1 to the extent of 59% of the total activity and C-9, 26%.[57] Thus, it appears that although acetate is able to act as an efficient precursor, it is undergoing extensive degradation *in vivo*. Pyruvate has been shown to be a more effective precursor of the two-carbon unit than acetate.[58] Administration of [3-^{14}C]pyruvate to *L. williamsii* gave radioactive anhalonidine (59) with activity spread over both C-1 and C-9 but with a major portion confined to C-9.

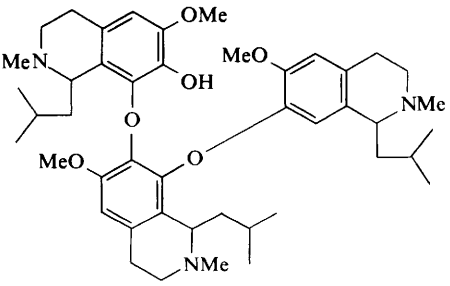
In agreement with the results obtained in *Lophocereus schottii* on the origin of the C_5 unit (C-1,1′,2′,3′,4′) in lophocerine (62),[59] a specific incorporation of [3′,4-^{14}C]mevalonic acid and [2-^{14}C]leucine was obtained into this alkaloid in *Pachycereus marginatus*.[60] Degradation revealed a labelling pattern consistent with an equal distribution between C-1′ and C-4′ plus C-3′ from the experiment

[57] A. R. Battersby, R. Binks, and R. Huxtable, *Tetrahedron Letters*, 1968, 611.
[58] E. Leete and J. D. Braunstein, *Tetrahedron Letters*, 1969, 451.
[59] D. G. O'Donovan and H. Horan, *J. Chem. Soc.* (*C*), 1968, 2791.
[60] H. R. Schütte and G. Seelig, *Annalen*, 1970, **730**, 186.

with mevalonic acid and a specific labelling of C-1 from the leucine feed. These two sets of results obtained in two different plants establish therefore a dual origin for this C_5 unit in lophocerine. A specific incorporation of [2-^{14}C]tyrosine into the remaining part of the molecule has also been obtained[59,60] and a high proportion of the activity resulting on administration of [*methyl*-^{14}C]methionine to *P. marginatus* was contained in the *O*- and *N*-methyl groups of lophocerine.[60]

The origin of the C_2 unit of (*e.g.*) pellotine (61) may conceivably be by degradation of a C_5 side chain, as is found in lophocerine.[57] It is notable that this idea is consistent with the established labelling of the C_2 unit by acetate[57] and pyruvate[58] if mevalonic acid is a precursor for the C_5 unit but not if leucine is.

Pilocereine (63) is isolated along with lophocerine from *L. schottii* and is manifestly the result of two phenol-coupling processes of three lophocerine units, and a 1% conversion of [*N-methyl*-^{14}C]lophocerine into the trimeric alkaloid has been demonstrated.[61] All the activity was confined to the *N*-methyl groups of (63).



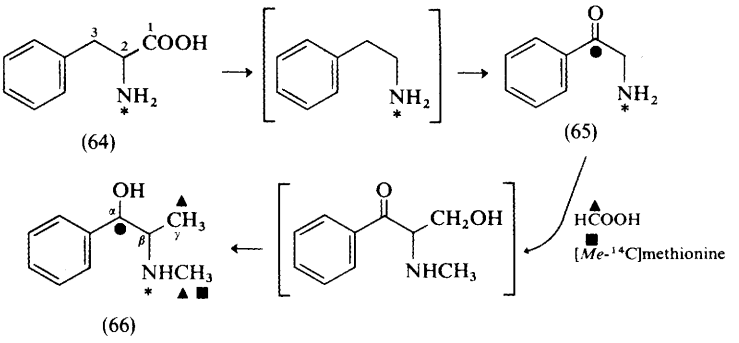
(63)

Ephedrine.—Earlier work by Shibata and his colleagues had produced a biosynthetic route (Scheme 8) for ephedrine (66) in *Ephedra distachya* which seemed well supported. Central to this scheme is the incorporation of C-2 of phenylalanine. This was tested recently and it was found that while C-3 and the aromatic ring of phenylalanine were incorporated into ephedrine, C-2 was not.[62] (A specific incorporation of [3-^{14}C]phenylalanine into norpseudoephedrine (67) had been recorded earlier.[63]) Confirmation of the utilisation of a C_6–C_1 rather than a C_6–C_2 unit was obtained with the specific incorporation of [*carboxyl*-^{14}C]-benzoate and [*carbonyl*-^{14}C]benzaldehyde; [3-^{14}C]cinnamate also labelled ephedrine specifically and all three precursors were more efficient than [3-^{14}C]phenylalanine.

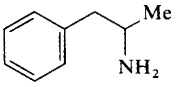
The origin of the β- and γ-carbon atoms is obscure: serine and alanine with uniform ^{14}C-labelling gave poor incorporation with randomisation over the

[61] D. G. O'Donovan and H. Horan, *J. Chem. Soc.* (*C*), 1969, 1737.
[62] K. Yamasaki, U. Sankawa, and S. Shibata, *Tetrahedron Letters*, 1969, 4099.
[63] E. Leete, *Chem. and Ind.*, 1958, 1088.

molecule. The earlier incorporations of [^{15}N]phenylalanine (64) and ω-aminoacetophenone (65) have been rationalised as transamination and ready decomposition to a C_6–C_1 unit respectively.



Scheme 8

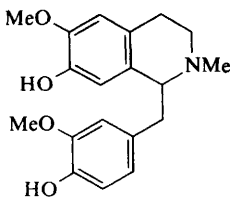


(67)

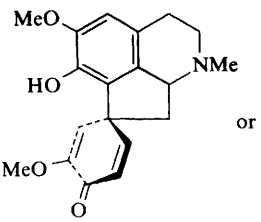
Benzylisoquinoline Alkaloids.—With the establishment of orientaline (68) and orientalinone (69) as precursors of isothebaine (71), it remained to test the likely possibility that reduction of orientalinone to a dienol followed by dienol–benzene rearrangement are involved in the final steps to (71). This has now been demonstrated.[64] Reduction of orientalinone gave orientalinols I and II (see 70) epimeric at C-10. These alcohols with tritium labelling at C-10 and the *N*-methyl group (the *N*-methyl group of orientaline was proved to survive biological transformation to isothebaine) were fed separately to *Papaver orientale*. Orientalinol-I was well incorporated (2.1 %) into isothebaine (71) with retention of ^{3}H from C-10 (76 %) whilst the II-isomer was poorly utilised (0.34 %) and the C-10 label was lost. Thus, orientalinol-I is proved to be the precursor of isothebaine. A redox conversion of the II-isomer into orientalinol-I would, it was pointed out, account for the results from the orientalinol-II feeding.

The mechanism of the dienol–benzene rearrangement has yet to be elucidated; the configurations of C-10 and C-13 of orientalinol-I (see 70) are unknown. In order to see if the product (72) of an allylic rearrangement could be interposed between orientalinol-I and isothebaine, ^{3}H-labelled (72) was fed as a mixture of dienols to *P. orientale*. No incorporation was found, but the significance of this is not clear as the configuration at the spiro centre is uncertain.

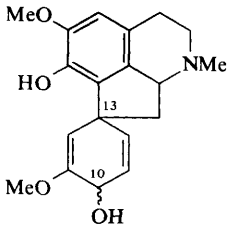
[64] A. R. Battersby, T. J. Brocksom, and R. Ramage, *Chem. Comm.*, 1969, 464.



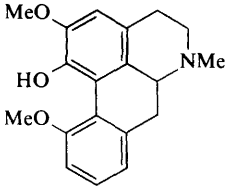
(68)



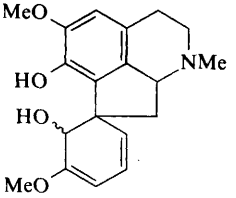
(69)



(70)

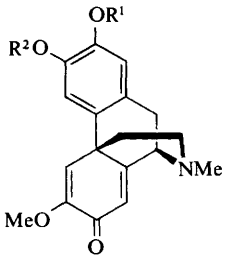


(71)

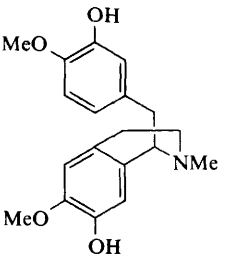


(72)

The dienone flavinantine (73) is found in *Croton flavens*. To distinguish between modes of coupling which could give (73), (±)-[*N-methyl*-^{14}C]reticuline (75) and similarly labelled (±)-orientaline (68) were administered to *C. flavens*.[65] Reticuline was found to be the favoured precursor for flavinantine (0.103% as against 0.012% for orientaline). No randomisation of the label from either precursor was apparent. Thus, the major route to this alkaloid would appear to involve a *para–para* oxidative coupling of reticuline to give isosalutaridine (74) which would give flavinantine by demethylation and remethylation in a manner analogous to that found in the biosynthesis of crotonosine.[66] [2-^{14}C]Phenylalanine was also incorporated into flavinantine and degradation showed that it was derived unexceptionally from two molecules of phenylalanine.

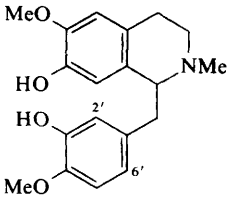


(73) R^1 = Me, R^2 = H
(74) R^1 = H, R^2 = Me

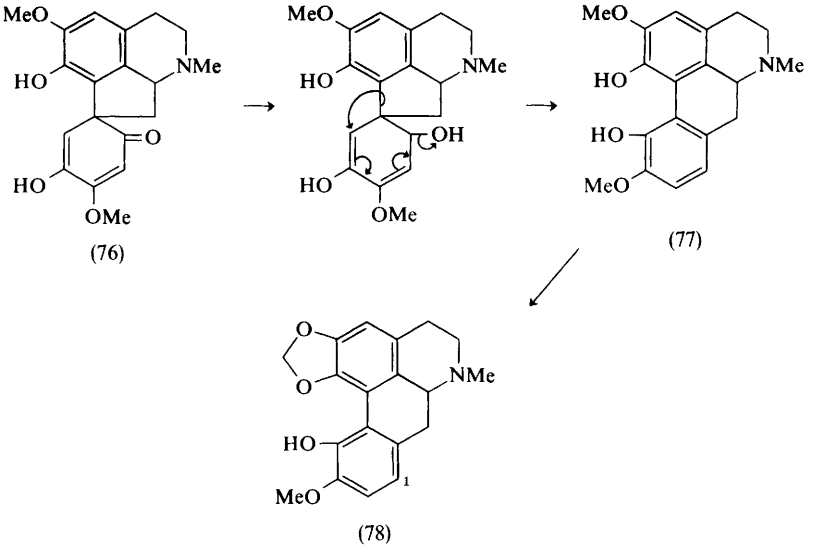


(75)

≡



[65] K. L. Stuart, V. Teetz, and B. Franck, *Chem. Comm.*, 1969, 333.
[66] D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, G. W. Kirby, L. J. Haynes, and K. L. Stuart, *J. Chem. Soc.* (*C*), 1967, 1295.



Scheme 9

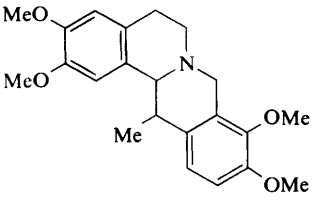
In contrast to the formation of isothebaine by a route involving a dienone, an alternative process is implicated in the biosynthesis of another aporphine alkaloid. Bulbocapnine (78) has been shown to be derived from reticuline (75).[67] The methylation pattern of reticuline implies a direct *ortho–ortho* phenol coupling in which corytuberine (77) is the first alkaloid to be formed. Further experiments[68] have been directed towards distinguishing this mode of coupling from an alternative pathway which involves hydroxylation of reticuline at C-6′ and formation of bulbocapnine *via* a biologically unknown dienone type (76, Scheme 9), a route which has been used in the chemical synthesis of aporphine alkaloids. [2′,6′-$^{3}H_2$, *N-methyl*-^{14}C]Reticuline (75), in which the proportions of tritium at the two positions were known, was fed to *Corydalis cava*. The bulbocapnine (78) isolated showed a $^{3}H : {}^{14}C$ ratio consistent only with complete retention of the C-6′ label at C-1 of bulbocapnine (78); the C-2′ label is, of course, lost during coupling. Corydaline (79) was also isolated in this experiment and showed a similar ^{3}H retention.

Thus, the formation of bulbocapnine is by a pathway involving direct *ortho–ortho* coupling of reticuline.

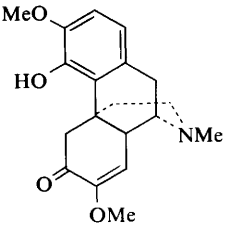
Phenol coupling of benzyltetrahydroisoquinolines *in vitro* may be strikingly more efficient if the nitrogen atom is protected as the quaternary salt.[69] It has been found, however, that in the *in vivo* synthesis of sinomenine (80) and

[67] G. Blaschke, *Arch. Pharm.*, 1968, **301**, 432.
[68] G. Blaschke, *Arch. Pharm.*, 1970, **303**, 358.
[69] B. Franck, G. Blaschke, and G. Sehlingloff, *Angew. Chem. Internat. Edn.*, 1964, **3**, 192 and references there cited.

protopine, (+)-reticuline is a better precursor than its methochloride,[70] which parallels the finding for morphine biosynthesis.[71] In each case a small incorporation of the metho-salt was found and this is presumably due to dequaternization to reticuline in the plant.



(79)



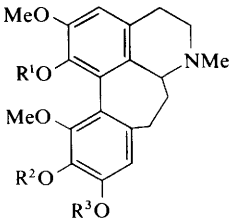
(80)

Homoaporphines.—The homoaporphine alkaloids, floramultine (81), multiflorine (82), and kreysigine (83), are isolated from *Kreysigia multiflora*. In order to test whether homoaporphines arise naturally by direct coupling of (*e.g.*) autumnaline (85) or by way of homoproaporphines, *e.g.* (88) or (89), the [3-^{14}C]phenethylisoquinolines (85), (86), and (87) were fed to *K. multiflora*.[72] The above three homoaporphines were isolated as *O*-methylkreysigine (84), after diazomethane methylation of the total alkaloid extract. Autumnaline (85) was well incorporated (1.6%) whilst (86) was a very poor precursor (0.014%) in accord with a mechanism involving direct coupling, with floramultine (81) the first to be formed. The compound (87) was incorporated into *O*-methylkreysigine (0.21%) presumably by way of autumnaline as is found in the biosynthesis of colchicine.[73] Degradation of the *O*-methylkreysigine from the autumnaline feed established a specific incorporation of this precursor. It is interesting to note that autumnaline is the immediate phenethylisoquinoline precursor of colchicine.[73]

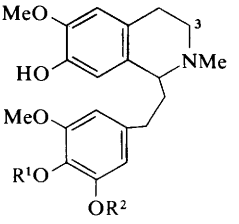
The results would appear then to exclude as a precursor for these homoaporphines kreysiginone (89) which, together with a dihydro-derivative, has been found in *K. multiflora*.[74]

***Erythrina* Alkaloids.**—The rôles of *N*-norprotosinomenine and erysodienone (92) as precursors for the *Erythrina* alkaloids have been further explored.[75] When

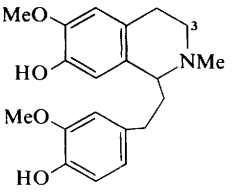
[70] D. H. R. Barton, R. B. Boar, D. A. Widdowson, V. Deulofeu, and S. M. Albonico, *J. Chem. Soc.* (*C*), 1969, 807.
[71] A. R. Battersby, D. M. Foulkes, M. Hirst, G. V. Parry, and J. Staunton, *J. Chem. Soc.* (*C*), 1968, 210.
[72] A. R. Battersby, P. Böhler, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1969, 1066.
[73] A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1966, 603; A. C. Barker, A. R. Battersby, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1967, 390.
[74] A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 934.
[75] D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1213.



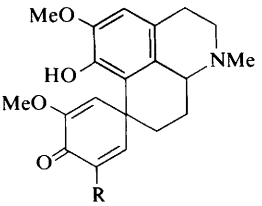
(81) $R^1 = R^3 = H$, $R^2 = Me$
(82) $R^1 = R^2 = H$, $R^3 = Me$
(83) $R^1 = H$, $R^2 = R^3 = Me$
(84) $R^1 = R^2 = R^3 = Me$



(85) $R^1 = Me$, $R^2 = H$
(86) $R^1 = H$, $R^2 = Me$



(87)

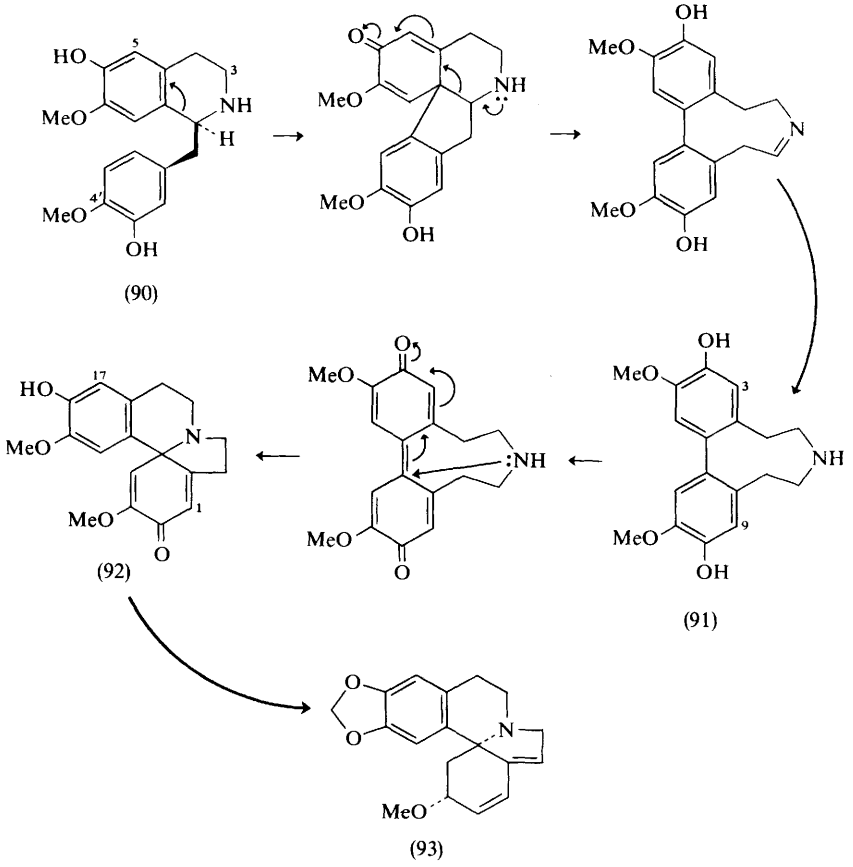


(88) R = OMe
(89) R = H

(+)-*N*-norprotosinomenine (90, with absolute stereochemistry as indicated), and its (−)-isomer, each with a ^3H label at position 5, were fed to *Erythrina crista galli*, only the former was significantly incorporated into erythraline (93) or erythratine (94). A similar result was obtained in the biosynthesis of erythraline from (+)- and (−)-[5-^{3}H,3-^{14}C]-*N*-norprotosinomenine and in addition the integrity of the $^3H : {}^{14}C$ ratio in the (+)-isomer was upheld in the alkaloid. The $^3H : {}^{14}C$ ratio was likewise unchanged in the conversion of [*O,O-dimethyl*-$^{14}C_2$,1,17-$^3H_2$]-erysodienone (92) into erythraline (93).

The base (91) is included in a suggested pathway to erythraline (Scheme 10) and its rôle as a precursor was tested in two experiments. Firstly, when (91) was fed with ^3H labels at positions 3 and 9 a good incorporation into erythraline (93) and erythratine (94) was obtained. Secondly, when this tritiated precursor was fed, mixed with material bearing ^{14}C labels in the methoxy-groups, no change in the $^3H : {}^{14}C$ ratio was found in the erythraline (93) isolated. Degradation revealed that the ^{14}C label was equally divided between the methoxy- and methylenedioxy-groups.

In the proposed biosynthetic route to erythraline (Scheme 10) loss of the initial asymmetry is apparent. In an examination of the stereochemical processes involved [4′-*methoxy*-^{14}C]-*N*-norprotosinomenine was administered to *E. crista galli*. The erythraline isolated showed an equal distribution of activity between the methoxy- and methylenedioxy-groups and so clearly the pathway involves a symmetrised intermediate, probably (91), and the asymmetry of erysodienone is not transferred from (90).

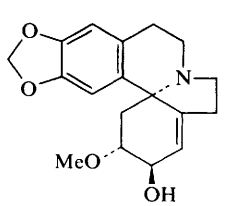


Scheme 10

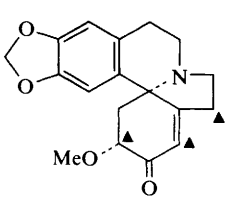
A good incorporation of amines (95)—(99), with tritium labelling as indicated, was obtained into erythraline (93). The results indicate, in contrast to the uniqueness of a methylation pattern required for phenol coupling, that for *Erythrina* at least the alkylation pattern during the later stages is not important.

Amaryllidaceae Alkaloids.—Chlidanthine (102) is an alkaloid of *Chlidanthus fragrans*. By analogy with the well-known conversion of codeine to morphine it might be expected to arise from galanthamine (101) by *O*-demethylation. This was shown to be true when both galanthamine and narwedine (100), with tritium labels, were incorporated into chlidanthine (102).[76]

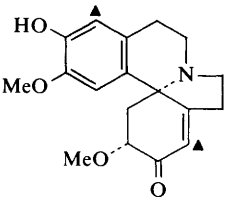
[76] J. G. Bhandarkar and G. W. Kirby, *J. Chem. Soc.* (*C*), 1970, 1224.



(94)



(95)



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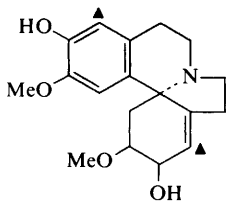

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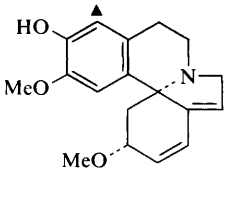

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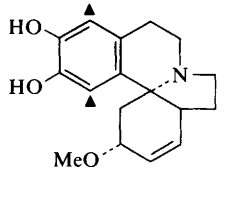
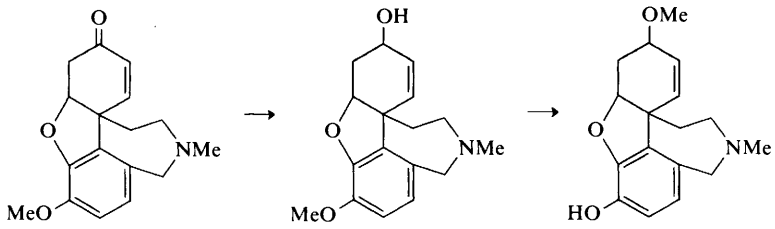


(99)

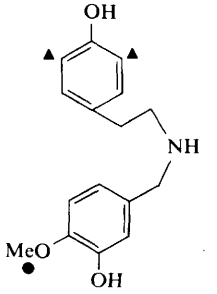
Although norbelladine was shown not to be a precursor of galanthamine (101) in 'King Alfred' daffodils, an incorporation of this compound with labels as shown (103), comparable to that for lycorine (104), has been obtained for galanthamine in *Leucojum aestivum*.[77] As expected, the lycorine showed loss of half its tritium. On the other hand, no loss of tritium was apparent in the galanthamine. The latter result suggested that in the biosynthesis of galanthamine conversion of (105) to narwedine (100) was either not reversible or, if so, enzymically controlled.

Incorporation of (103, labelled as shown), into haemanthamine (106) is without loss of tritium, half of which is sited at C-2.[78] Aromatisation of ring C *via* 11-oxohaemanthamine with either t-butoxide or in a Hofmann reaction gave differing tritium retentions. Consideration of the possible mechanisms involved in relation to tritium retention led to the suggestion that the tritium which is expected at C-4 might not be stereospecific.[79]

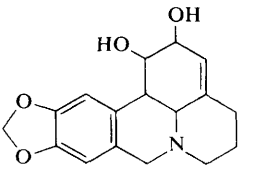


(100) (101) (102)

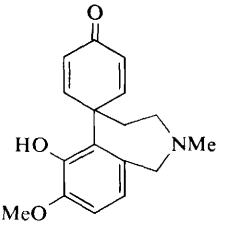
[77] C. Fuganti, *Chimica e Industria*, 1969, **51**, 1254, paper 1.
[78] A. R. Battersby, C. Fuganti, and J. Staunton, to be published.
[79] C. Fuganti, *Chimica e Industria*, 1969, **51**, 1254, paper 2.



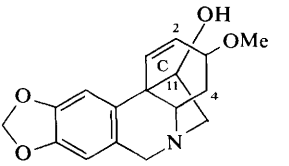
(103) (● : ^{14}C; ▲ : ^{3}H)



(104)



(105)



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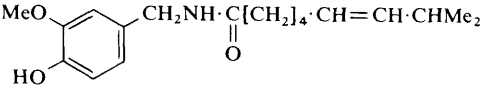
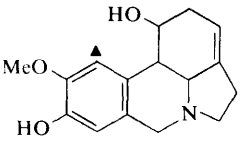
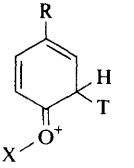


(107)



(108)



(109)

The biological conversion of cinnamic acid *via* hydroxylated cinnamic acids into the C_6–C_1 units of capsaicin (107) and norpluviine (108) has been used in a study of hydroxylation mechanisms in higher plants.[80]

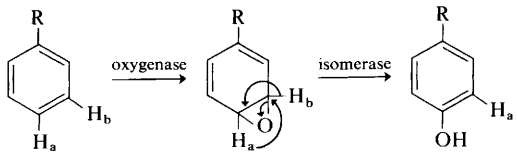
When [4-^{3}H,β-^{14}C]cinnamic acid was fed to *Capsicum annuum*, the derived capsaicin (107) showed a 50% tritium retention with essentially all of this label

[80] W. R. Bowman, I. T. Bruce, and G. W. Kirby, *Chem. Comm.*, 1969, 1075.

ortho to the phenolic hydroxy-group. This was consistent with (*a*) *para*-hydroxylation of the cinnamic acid and a virtually complete 1,2-shift of tritium with retention ('NIH' shift) and (*b*) a second hydroxylation at one of two equivalent positions causing loss of half the remaining tritium. These results are in accord with previous work on other aromatic substrates, which had shown further that the high retention of tritium observed in the first hydroxylation was reasonably the consequence of a large isotope effect operating in the aromatisation of an intermediate (109).[81] However, the tritium retention in capsaicin was the same when [3,5-$^{2}H_2$,4-^{3}H,β-^{14}C]cinnamic acid was a precursor. As a T/H isotope effect must be larger than a T/D isotope effect, (109) could not be an intermediate unless hydrogen loss was stereospecific.

Similar results were found in 'Texas' daffodils for the biosynthesis of norpluviine (108); the site of ^{3}H labelling is indicated. Further, tritium retention in norpluviine derived from [3-^{3}H,β-^{14}C]cinnamic acid was 28%. This agrees well with a predicted value of 25% resulting from *para*-hydroxylation with *hydrogen* migration and retention, where half the tritium would be lost in the first hydroxylation and half the remainder in the second.

These results show then that in the introduction of the first hydroxy-group on an aromatic substrate, hydrogen loss after 1,2-migration is stereospecific rather than isotopically controlled and it is the migrating hydrogen which is retained. Lack of the appropriate enzyme(s) in the previous experiments (which were with purified or partially purified enzyme systems) would account for results differing from those found in the intact plant. These results were accommodated within a plausible sequence (Scheme 11) which finds *in vitro* support.[82] The intermediate (109) may be included, provided hydrogen loss is enzymically controlled and thereby stereospecific.



Scheme 11

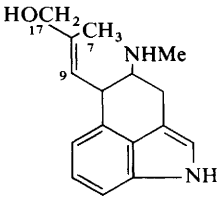
Ergot.—When [17-^{3}H,^{14}C]chanoclavine-I (110) was administered to *Claviceps*, the elymoclavine (112) isolated showed a 53% tritium retention, indicating that in the conversion of (110) to (112) one of the methylene hydrogens at C-17 is lost.[83] This suggested the possible intermediacy of chanoclavine-I-aldehyde (111) in this sequence, and indeed (111) with a C-17 tritium label was significantly better incorporated into elymoclavine than was chanoclavine-I; the tritium

[81] G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, 1967, **157**, 1524 and references cited. See also, further references cited in ref. 76.

[82] D. M. Jerina, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, 1968, **90**, 6523; D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltman-Nirenberg, and S. Udenfriend, *ibid.*, p. 6525.

[83] B. Naidoo, J. M. Cassady, G. E. Blair, and H. G. Floss, *Chem. Comm.*, 1970, 471.

label was confined to C-7 as expected. Further, [17-^{3}H,^{14}C]chanoclavine-I-aldehyde (111) was incorporated with little loss of tritium. Thus, this aldehyde (111) is a specific precursor for elymoclavine (112) and a likely natural intermediate.



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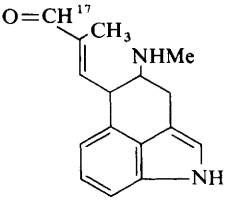
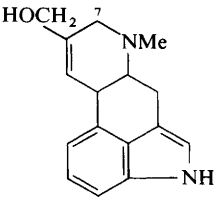


(111)



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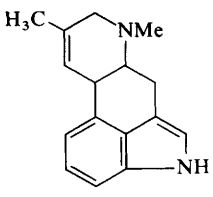

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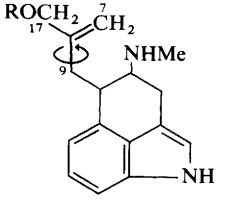

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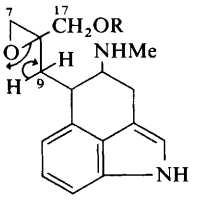


(115)

The conversion of chanoclavine-I into elymoclavine by use of a cell-free system obtained from *Claviceps* has also been examined.[84] A good conversion of (110) into (112) was obtained but agroclavine (113), which is accepted as an intermediate in this transformation *in vivo*, could not be detected. Further, agroclavine was poorly used as a precursor for elymoclavine (112) in this system.

The enzyme system used needed free oxygen and NADPH for the conversion of (110) to (112), suggesting the involvement of a mono-oxygenase and, indeed, oxygenases appear to be implicated in ergot alkaloid biosynthesis *in vivo*.[85] This, together with an observed proton loss from C-9 of (110) during *in vivo* transformation to (112),[86] suggested the sequence (110) → (114) → (115) → (112). The need for ATP for the reaction in the cell-free system allowed ring-closure at some point in this sequence by nucleophilic displacement of phosphate. This mode of ring-closure, however, does not accommodate loss of a C-17 proton [and the intermediacy of chanoclavine-I-aldehyde (111)].[83]

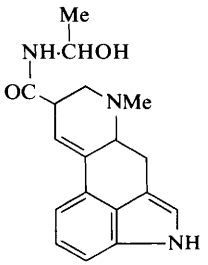
A plausible precursor for lysergic acid α-hydroxyethylamide (116) is lysergyl-alanine (117). Administration of D-lysergyl-L-alanine with a ^{14}C label as shown in (117) to *Claviceps paspali*, however, gave an enhanced yield of ergometrine (118) and very little radio-activity in the side chain of (116); degradation of the ergometrine showed that the label was confined to C-2 plus C-3 of the alaninol

[84] E. O. Ogunlana, B. J. Wilson, V. E. Tyler, and E. Ramstad, *Chem. Comm.*, 1970, 775.
[85] E. O. Ogunlana, E. Ramstad, and V. E. Tyler, *J. Pharm. Sci.*, 1969, **58**, 143.
[86] H. G. Floss, U. Hornemann, N. Schilling, K. Kelley, D. Gröger, and D. Erge, *J. Amer. Chem. Soc.*, 1968, **90**, 6500.

side chain.[87] Thus, lysergylalanine is a precursor for ergometrine but not for lysergic acid α-hydroxyethylamide; as alanine is utilised by *C. paspali* in ergometrine synthesis with substantial labelling of the ring system, (117) is converted to (118) intact.

The possibility that ergometrine might be a precursor for ergotamine (119) has been tested in *C. purpurea*.[88] Whilst lysergic acid was well incorporated into ergotamine and ergokryptine, ergometrine was not. Ergometrine was also shown not to be precursor for lysergic acid α-hydroxyethylamide (116) in *C. paspali*, whereas lysergic acid was efficiently utilised. Alanine and alaninol served as similarly effective precursors for (116) but alaninol was clearly better than alanine as a precursor for ergometrine (118).

This latter result is in conflict with other results where alanine was shown to be incorporated into ergometrine but alaninol was not.[89] Neither is α-methylserine, which might give alaninol by decarboxylation, utilised.



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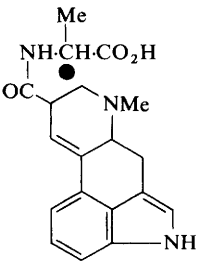

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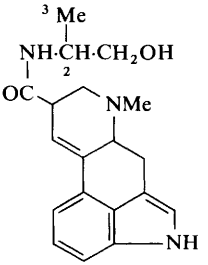

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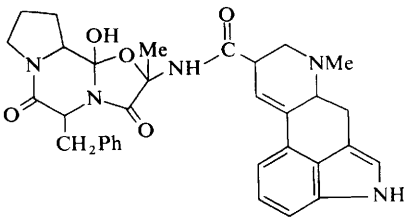

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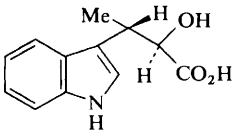

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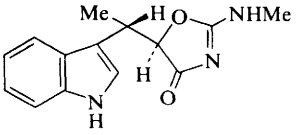


(121)

[87] G. Basmadjian, H. G. Floss, D. Gröger, and D. Erge, *Chem. Comm.*, 1969, 418.
[88] A. Minghetti and F. Arcamone, *Experientia*, 1969, **25**, 926.
[89] U. Nelson and S. Agurell, *Acta Chem. Scand.*, 1969, **23**, 3393.

Indolmycin.—Of the four optical isomers of indolmycenic acid which might serve as precursors for indolmycin (121), only the naturally occurring isomer (120), with the same absolute stereochemistry as indolmycin, is significantly incorporated in *Streptomyces griseus*.[90]

[90] U. Hornemann, L. H. Hurley, M. K. Speedle, and H. G. Floss, *Tetrahedron Letters*, 1970, 2255.

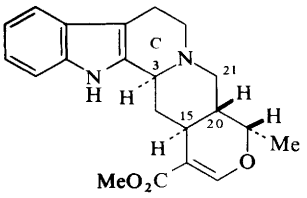
2

Biosynthesis—II. Terpenoid Indole Alkaloids[1]

BY A. R. BATTERSBY

This chapter will review the progress which has been made over the last five years or so in understanding the biosynthesis of indole alkaloids comprising the *Corynanthe–Strychnos*, *Aspidosperma*, and *Iboga* families. Other indole alkaloids, *e.g.* those of the ergot group, are covered in Chapter 1. It is a fortunate time to prepare a survey for though there are still many fascinating problems awaiting solution in this area, the major challenges presented by the indole alkaloids, say in 1960, have all been met.

Researches carried out to the early part of 1966 have been comprehensively reviewed[2] and the present account will set out from that point. In brief, the situation reached at that time was as follows. Despite their bewildering variety, three main groups of alkaloids had been recognised: (*a*) the *Corynanthe-Strychnos* type, *e.g.* ajmalicine (1) and akuammicine (2) which possess the non-tryptamine unit (3), (*b*) the *Aspidosperma* type, *e.g.* vindoline (4), in which the non-tryptamine unit appears as (5), and (*c*) the *Iboga* type, *e.g.* catharanthine (6), having still a different arrangement[3] of the non-tryptamine unit (7).



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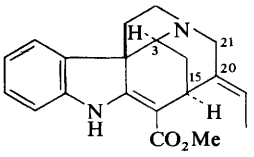

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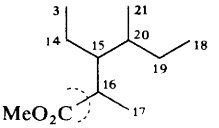
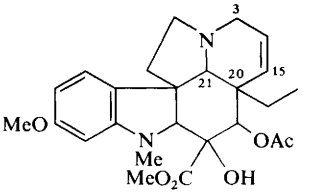


(3)

[1] Dedicated to Professor K. Mothes on the occasion of his seventieth birthday.

[2] A. R. Battersby, *Pure and Applied Chem.*, 1967, **14**, 117.

[3] The numbering system is that of W. I. Taylor and J. LeMen, *Experientia*, 1965, **21**, 508.



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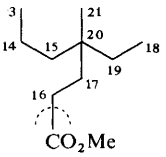

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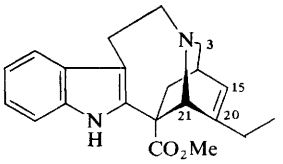

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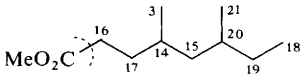
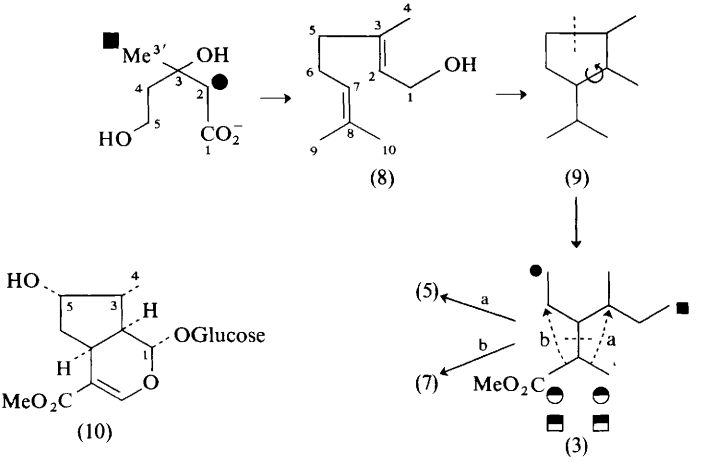


(7)

These non-tryptamine units almost always contain ten or nine skeletal carbon atoms (hence the term C_9—C_{10} unit) and in the latter case it is invariably the atom indicated by the dotted line which has been lost. The tryptamine portion of these molecules is derivable *in vivo* from tryptophan, and recent work has demonstrated that tryptamine is an effective precursor of the alkaloids.[33—35] Further, as the result of an enormous effort by three research groups, it was shown that all three types of C_9—C_{10} unit (3), (5), and (7) are monoterpenoid in origin. Two residues of mevalonate are used biologically in the normal head-to-tail combination of C_5 units and the intermediacy of geraniol (8) was established. The ^{14}C-labelling patterns were determined for representatives of the three types of alkaloid biosynthesised from labelled mevalonates which carried specific ^{14}C labels at various known positions. The results were consistent with the proposal of Thomas and Wenkert that (3) is generated by fission of some cyclopentane monoterpene (9) with rotation about the indicated single bond as in Scheme 1. It was further recognised that unit (3) is structurally related to (5) and (7) and can be mentally transformed into these other types by the bond fission and bond formation either at (a) or (b), Scheme 1. The *Aspidosperma* and *Iboga* families are thus often referred to as rearranged systems. It must be mentioned that the incorporation of [2-^{14}C]mevalonate resulted in a randomisation of the label in the two terminal positions (see Scheme 1); *i.e.*, the carboxyl carbon carried *ca.* 25% of the total activity, rather than 50% or 0%. This loss of identity of the two terminal carbons was confirmed[22] by showing that [3'-^{14}C]-mevalonate caused labelling (*ca.* 20% of the total) at the ester carbonyl groups of (1), (4), and (6). Finally, an important intermediate on the pathway to these alkaloids was defined when the cyclopentane monoterpene (9), shown as a skeleton only, was proved to be loganin (10). These results and reasoning based upon structural relations led to the proposal[2] of Scheme 2 as the early and middle parts of the pathway to indole alkaloids.



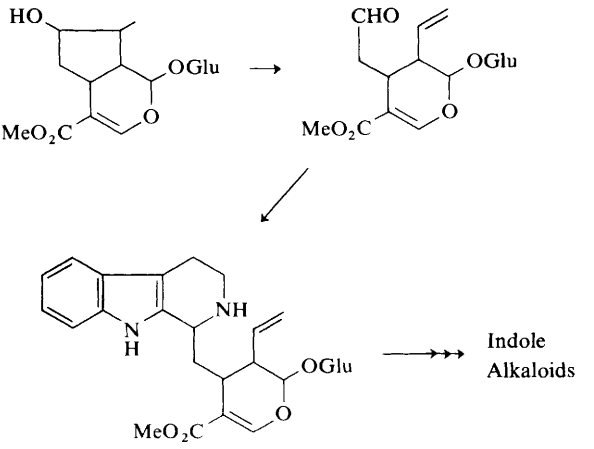
Scheme 1

Several papers have appeared[4—9] since the earlier review[2] which either confirm in various ways the points summarised above or describe more fully experiments previously reported only briefly.

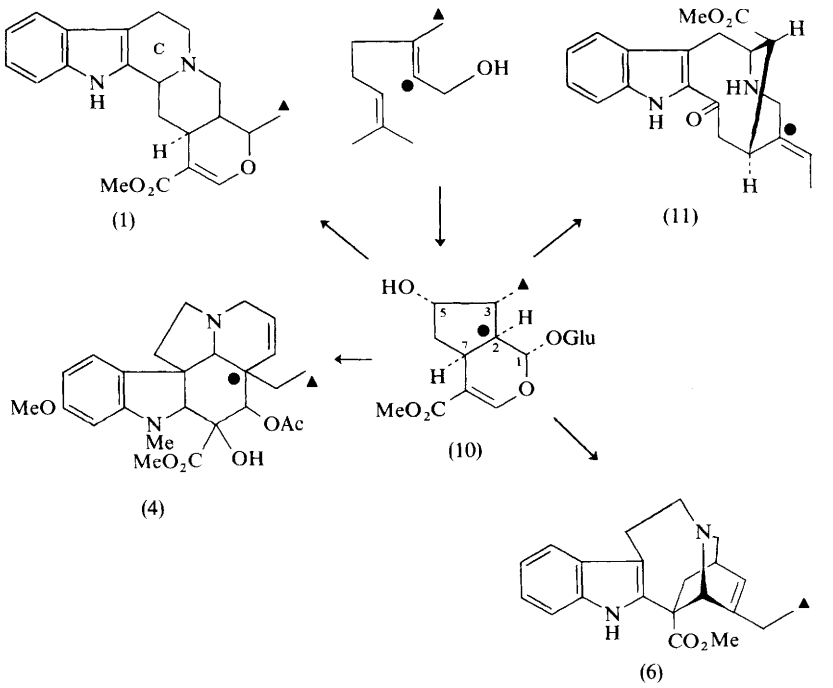
The foregoing work with loganin was based upon [*O-methyl*-^{3}H]-labelled material[6] and was extended by biosynthetic conversion (using *Menyanthes trifoliata* plants) of [2-^{14}C]geraniol and [4-^{14}C]geraniol into two samples of skeletally-labelled loganin. These were fed separately to *Vinca rosea* shoots and the labelling patterns found[10,11] for the isolated alkaloids are shown combined in Scheme 3; structure (11) is perivine. Further evidence came[10] from similar biosynthetic conversion of [1-$^3H_2$]geraniol into [1-^{3}H]loganin which was then incorporated into ajmaline (12) by *Rauwolfia serpentina* plants; degradation of the alkaloid showed specific labelling at the illustrated site. These experiments rigorously confirmed that loganin is a specific precursor of all three types of indole alkaloid. Moreover, loganin was proved to be present in *Vinca rosea* by dilution analysis[6,11] and by direct isolation.[12]

Though at the time of the foregoing work loganin was a fully characterised substance, its structure had not been rigorously established and its stereochemistry was unknown. Accordingly, chemical correlations of loganin with

[4] D. Gröger, K. Stolle, and K. Mothes, *Z. Naturforsch.*, 1966, **21b**, 206.
[5] A. R. Battersby, R. T. Brown, R. S. Kapil, J. A. Knight, J. A. Martin, and A. O. Plunkett, *Chem. Comm.*, 1966, 888.
[6] A. R. Battersby, R. T. Brown, R. S. Kapil, J. A. Martin, and A. O. Plunkett, *Chem. Comm.*, 1966, 890.
[7] E. Leete and S. Ueda, *Tetrahedron Letters*, 1966, 4915.
[8] D. Gröger, K. Stolle, and K. Mothes, *Arch. Pharm.*, 1967, **300**, 393.
[9] T. Money, I. G. Wright, F. McCapra, E. S. Hall, and A. I. Scott, *J. Amer. Chem. Soc.*, 1968, **90**, 4144.
[10] A. R. Battersby, R. S. Kapil, J. A. Martin, and L. Mo, *Chem. Comm.*, 1968, 133.
[11] P. Loew and D. Arigoni, *Chem. Comm.*, 1968, 137.
[12] A. R. Battersby, A. R. Burnett, E. S. Hall, and P. G. Parsons, *Chem. Comm.*, 1968, 1582.



Scheme 2

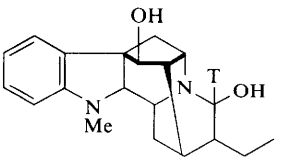


Scheme 3

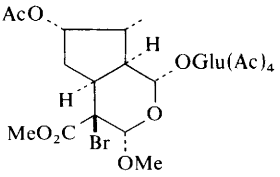
substances of proven structure and absolute configuration were carried out, together with optical and n.m.r. studies which led to the complete representation (10) for the glucoside.[13—16] This has recently been confirmed in every detail by *X*-ray analysis of the methoxybromide (13).[17]

It has been implicit in the discussion so far that geraniol is incorporated specifically into loganin. It was important, however, to have direct evidence, and this came from degradation[11] of the above loganin derived from [4-^{14}C]geraniol and by suitable oxidation and ^{3}H-exchange experiments[14] on labelled loganin biosynthesised in *Vinca rosea* plants from [6-$^{3}H_2$,2-^{14}C]geraniol. In both cases, the labelling of loganin was entirely at the expected site.

The biosynthetic stages between geraniol and loganin (Scheme 4) have been examined by working back from loganin and forward from geraniol. Arguments based upon structural relations pointed towards deoxyloganin (18) as the immediate precursor of loganin. Proof that this is so came (*a*) from the preparation of [4-^{3}H]deoxyloganic acid (17) from asperuloside and its specific incorporation by *Lonicera japonica* plants into loganin,[18] and (*b*) by partial synthesis of [*O-methyl*-^{3}H]deoxyloganin (18) from loganin and demonstration of its incorporation without randomisation of the label into loganin and the indole alkaloids (1), (4), (6), and (11) together with serpentine[19,20] [as (1), ring C



(12)



(13)

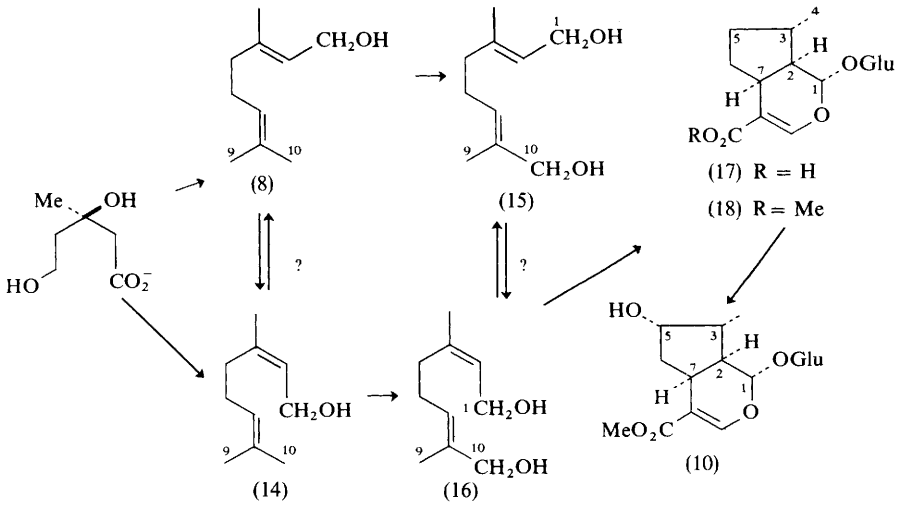
aromatised]. *Vinca rosea* plants were used for experiment (*b*). In addition, deoxyloganin was shown by dilution analysis[20] to be present in *Menyanthes trifoliata*, a plant rich in loganin, and also in *Vinca rosea*. Large scale extraction of the latter plant and also *Strychnos nux vomica* fruit yielded, after acetylation, crystalline deoxyloganin tetra-acetate.[20]

It is interesting in connection with the above incorporation of deoxyloganic acid into loganin that loganic acid [acid corresponding to (10)] has been isolated

[13] A. R. Battersby, R. S. Kapil, and R. Southgate, *Chem. Comm.*, 1968, 131.
[14] A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc.* (*C*), 1969, 721.
[15] S. Brechbühler-Bader, C. J. Coscia, P. Loew, Ch. von Szczepanski, and D. Arigoni, *Chem. Comm.*, 1968, 136.
[16] H. Inouye, T. Yoshida, and S. Tomita, *Tetrahedron Letters*, 1968, 2945.
[17] P. J. Lenz and M. G. Rossmann, *Chem. Comm.*, 1969, 1269.
[18] H. Inouye, S. Ueda, Y. Aoki, and Y. Takeda, *Tetrahedron Letters*, 1969, 2351.
[19] A. R. Battersby, 'Natural Substances formed biologically from Mevalonic Acid,' ed. T. W. Goodwin, Academic Press, London, 1970, p. 157.
[20] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *Chem. Comm.*, 1970, 826.

from *Swertia caroliniensis*. When [2-^{14}C]mevalonate and [1-^{14}C]geranyl pyrophosphate were fed to these plants, radioactive loganic acid was isolated.[21]

Forward exploration along the pathway from geraniol, or nerol (14) which is almost as effective a precursor of loganin as geraniol,[5] was carried out in two laboratories and was guided by the following argument. It is evident that the conversion of geraniol or nerol into deoxyloganin involves oxidation of C-1 to aldehydic level, oxidation of the C-9 and C-10 methyl groups, saturation of the Δ^2-olefinic residue, and formation of the cyclopentane ring and various sequences are conceivable, some combining the two steps last in the list. However, the occurrence alongside loganin of monoterpenes oxidised at C-10 in *Menyanthes trifoliata* (see later) together with mechanistic considerations pointed to oxidation at C-10 as the primary step. One group[22] synthesised [9-^{14}C]-10-hydroxygeraniol (15) and [9-^{14}C]-10-hydroxynerol (16) which were administered separately to



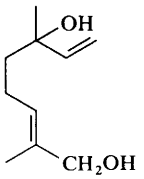
Scheme 4

Vinca rosea plants. Both substances (Scheme 4) were incorporated specifically into loganin (10), ajmalicine (1), vindoline (4), and catharanthine (6) with the *cis*-compound (16) generally being more effective than the *trans*-isomer (15). The methoxycarbonyl groups of the isolated radioactive materials contained, in each case, *ca.* 40—48% of the total activity showing the occurrence of extensive, if not complete, randomisation in the terminal units of (15) and (16). Thus, the equilibration process must involve introduction of oxygen at both C-9 and C-10 of geraniol or nerol. It was further shown[22] that labelled (19), (20), and (21)

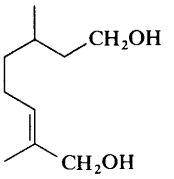
[21] C. J. Coscia and R. Guarnaccia, *Chem. Comm.*, 1968, 138.
[22] S. Escher, P. Loew, and D. Arigoni, *Chem. Comm.*, 1970, 823 and reference 2 therein.

are not significantly incorporated into loganin and/or the indole alkaloids by *Vinca rosea* shoots.

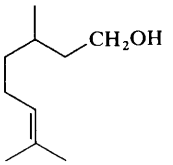
The synthetic route used by the other group[23] led to [1-$^3H_2$]-10-hydroxygeraniol (15) and [1-$^3H_2$]-10-hydroxynerol (16) which were administered together to *Vinca rosea* plants. Good incorporations were observed into loganin (10), ajmalicine (1), serpentine [(1), ring C aromatised], vindoline (4), catharanthine (6), and perivine (11). Compounds (20) and (21) were not appreciably incorporated[23] into loganin or any of the foregoing alkaloids in agreement with the researches outlined above. In addition,[23] compounds (22), (23), (24), and (25) failed to act as precursors and, in a separate study,[24] (26) proved ineffective.



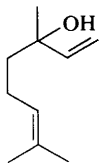
(19)



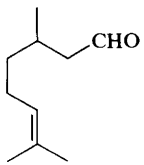
(20)



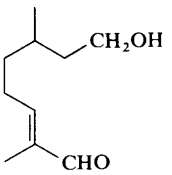
(21)



(22)



(23)



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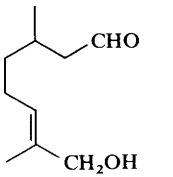
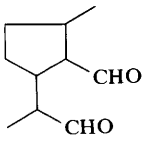


(25)

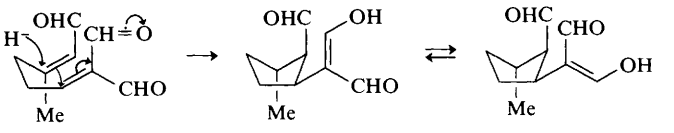


(26)

The sum of the foregoing evidence greatly restricts the range of possible biosynthetic intermediates beyond (15) and (16). Available knowledge is best accommodated[22] by Scheme 5 for the cyclisation step; in particular, the observed terminal randomisation is rationalised.[25]

Three approaches can be considered in order to discover the biosynthetic intermediates which lie on the pathway between loganin and the indole alkaloids. One is to decide on chemical, structural, and biosynthetic grounds what the probable intermediates are and then to prepare these substances by synthesis or biosynthesis for test as precursors of the alkaloids. A second approach is to determine the changes in oxidation level which occur at the various carbon atoms of the loganin skeleton as it is transformed through the many stages leading to the three families of alkaloids. Clearly this involves extensive use of tritium labelling and the results put strict limitations on the biosynthetic schemes which can be considered; in addition, they provide information about the mechanisms

[23] A. R. Battersby, S. H. Brown, and T. G. Payne, *Chem. Comm.*, 1970, 827.
[24] E. Leete and R. M. Bowman, *Phytochemistry*, 1969, **8**, 1003.
[25] *cf.* D. A. Yeowell and H. Schmid, *Experientia*, 1964, **20**, 250.

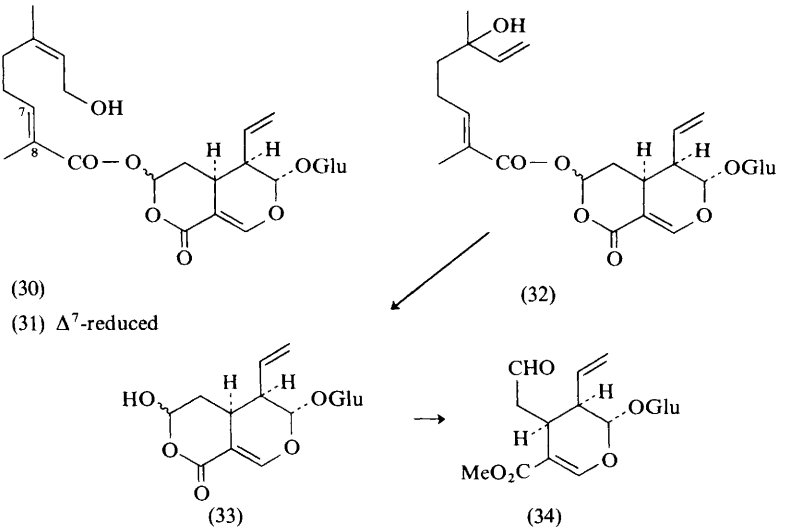


(27) (28) (29)

Scheme 5

of the various reactions. The third method involves direct isolation of intermediates combined with studies of sequence of formation of alkaloids in young plants. All three approaches have been used over recent years and they have been mutually helpful.

Scheme 2 showed two substances which, it was argued,[2] were probable intermediates beyond loganin. The possibility of studying these two materials was opened by the isolation of new glucosides foliamenthin and menthiafolin from *Menyanthes trifoliata*.[26,27] The former glucoside was proved[26] to have structure (30) and by drawing on the results for (30) the latter was shown[27] to have structure (32). In addition, dihydrofoliamenthin (31) was isolated from the plants.[26,27] Hydrolysis of menthiafolin (32) yielded (33) which was of decisive importance in that it represents the required aldehyde (34) in a masked lactol form. Ring-opening and methylation gave (34), now known as secologanin.[28,29] [*O-methyl-*



(30)

(31) Δ^7-reduced

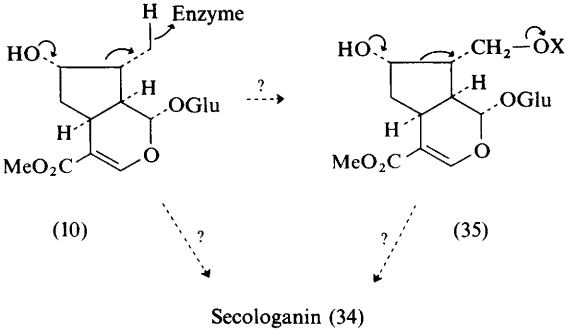
(32)

(33) (34)

[26] P. Loew, Ch. von Szczepanski, C. J. Coscia, and D. Arigoni, *Chem. Comm.*, 1968, 1276.
[27] A. R. Battersby, A. R. Burnett, G. D. Knowles, and P. G. Parsons, *Chem. Comm.*, 1968, 1277.
[28] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *Chem. Comm.*, 1968, 1280.
[29] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1187.

^{3}H]Secologanin was incorporated by *Vinca rosea* well and without randomisation of the label into representative examples of all three families of indole alkaloids. Having the partially synthetic secologanin available as a marker for fractionations also allowed its isolation from *Vinca rosea* both by radiochemical dilution analysis and by macro-isolation as a crystalline derivative.[28,29] Secologanin was thus shown to be a natural product and its status as a precursor of indole alkaloids was secure. More recently, secologanin has also been found in *Lonicera morrowii*.[30] It seems highly probable that secologanin (34) will be the parent of a large range of cleaved cyclopentane monoterpenes. An indication comes from the proof[31] that secologanin acts as precursor of the three glucosides (30), (31), and (32), and also of sweroside (36) in *Menyanthes trifoliata*.

Experiments in both *Vinca rosea* and *Menyanthes trifoliata*[29] demonstrated the specific cleavage of [*O-methyl*-^{3}H]loganin (10) to give [*O-methyl*-^{3}H]secologanin (5—6% incorporation). The mechanism of the C–C bond fission is of considerable interest and two possibilities illustrated in Scheme 6 have been



Scheme 6

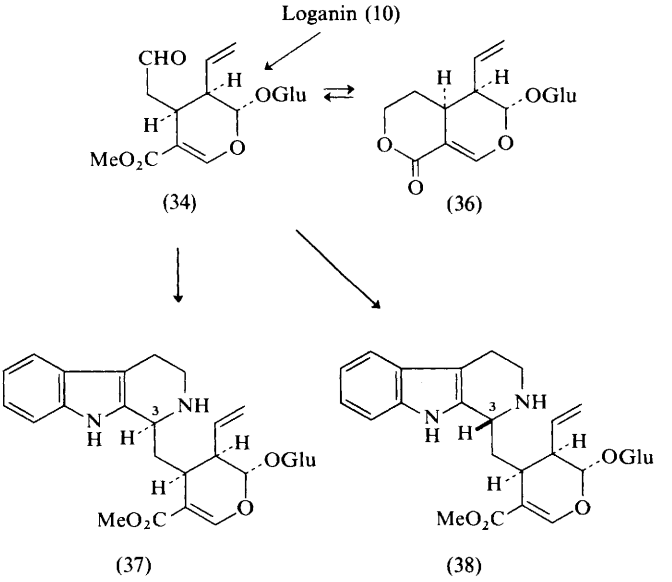
considered: (*a*) direct fragmentation initiated effectively by hydride abstraction by the enzyme system involved, and (*b*) a first step of hydroxylation at saturated carbon to generate hydroxyloganin (35, X = H) followed by fragmentation of a suitable derivative (presumably phosphate ester).

The specific incorporation[32] of [4-^{14}C]sweroside into vindoline (4) seems best understood by interconversion of secologanin (34) and sweroside (36). The biological change (34) → (36) was shown above and the reverse was proven by feeding [6-$^{3}H_2$]sweroside to *Vinca rosea* and isolating therefrom [6-$^{3}H_2$]secologanin;[31] specific labelling was proven.

Condensation of tryptamine with secologanin opened the way to studies of the later stages of the biosynthesis. Two basic glucosides, vincoside and

[30] I. Souzu and H. M. Mitsuhashi, *Tetrahedron Letters*, 1970, 191.
[31] A. R. Battersby, A. R. Burnett, and P. G. Parsons, unpublished work.
[32] H. Inouye, S. Ueda, and Y. Takeda, *Tetrahedron Letters*, 1968, 3453.

isovincoside, having structures and absolute configurations (37) and (38) were obtained.[33,34] Though the available evidence seemed best accommodated by assigning (37) to vincoside and (38) to isovincoside, rigorous evidence concerning the only remaining uncertain point, the C-3 configuration, is being sought by *X*-ray analysis. Doubly labelled [*Ar*-^{3}H, *O-methyl*-^{3}H]vincoside was incorporated well by *Vinca rosea* plants into all three types of indole alkaloid without change in the ratio of the two labels;[33,34] isovincoside was biologically inert and afforded no significant incorporations into any of the alkaloids.[12] These results show that the main skeleton of vincoside (*i.e.* without the glucose residue) is built intact into the *Corynanthe*, *Aspidosperma* and *Iboga* systems. This biological conversion of the *Corynanthe*-type C_{10}-unit of vincoside into the rearranged systems of *Aspidosperma* and *Iboga* was of interest.[35]



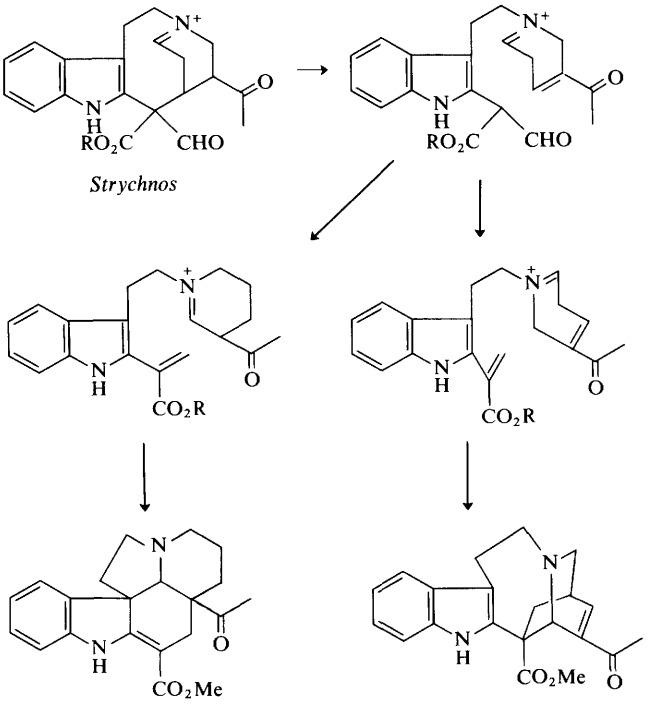
Scheme 7

Macro-isolation and radiochemical dilution analysis based upon the incorporation of [5-^{3}H]loganin proved that both vincoside and isovincoside are present in *Vinca rosea* plants, and *N*-acetylvincoside was also isolated.[33,34] Independently and simultaneously with the above work, strictosidine[36] was isolated from *Rhazya stricta*, was proved to be present by dilution analysis in

[33] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *Chem. Comm.*, 1968, 1282.
[34] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1193.
[35] J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, 1968, **90**, 3566.
[36] G. N. Smith, *Chem. Comm.*, 1968, 912.

Vinca rosea[37] and was shown to have the gross structure of (37) or (38). [*O*-methyl-^{3}H]Loganin was specifically incorporated into strictosidine.[37] Direct comparisons have established the identity of strictosidine and isovincoside.[38]

Before reviewing the biosynthetic pathway beyond vincoside, the contributions of arguments[39] based upon structural relations at the alkaloidal level should be outlined. Two points have been particularly helpful: (*a*) it was held that there must be biosynthetic significance to the observation that there is almost complete stereochemical constancy at C-15 in the *Corynanthe-Strychnos* group which matched that at the corresponding position of the then known cyclopentane monoterpenes, and (*b*) it was argued that the *Strychnos*, *Aspidosperma*, and *Iboga* alkaloids could be derived from the *Corynanthe* system. The *structural* relationship of the *Strychnos* to *Aspidosperma* and *Iboga* skeletons is shown in Scheme 8 which includes mechanistic speculations.[39] It will be seen later that



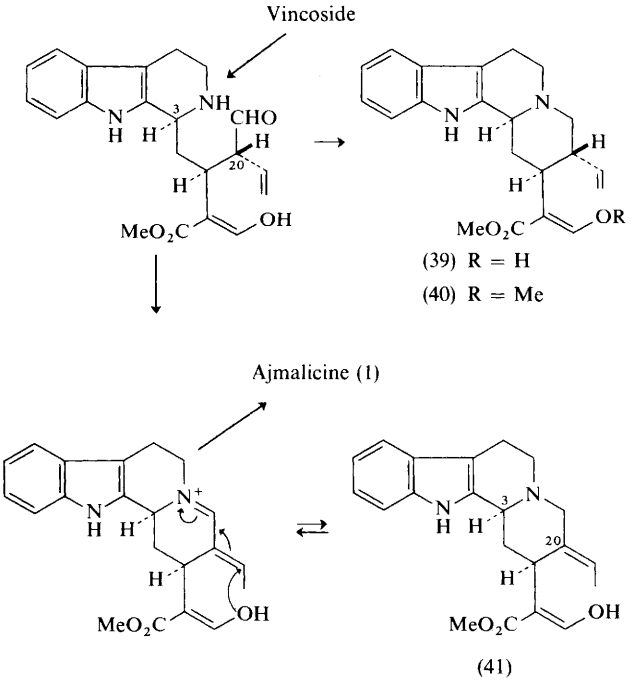
Scheme 8

[37] R. T. Brown, G. N. Smith, and K. S. J. Stapleford, *Tetrahedron Letters*, 1968, 4349.
[38] A. R. Burnett, P. G. Parsons, and G. N. Smith, personal communication.
[39] E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.*, 1959, **81**, 1474; E. Wenkert, *J. Amer. Chem. Soc.*, 1962, **84**, 98; E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, 1965, **87**, 1580.

these mechanisms need to be changed in the light of direct biosynthetic information but the skeletal relationships are, in essence, correct.

Returning to the pathway beyond vincoside, formation of the *Corynanthe* family requires no skeletal rearrangement and is regarded as involving enzymatic cleavage of glucose as a first step as in Scheme 9.[34,40] Geissoschizine (41), corynantheine (40) and its aldehyde (39), and ajmalicine (1) are then derivable by plausible steps.

The sum of the foregoing work and reasoning make corynantheine aldehyde (39) and geissoschizine (41) clear candidates for test as precursors of the other alkaloidal systems. Further evidence also came at this stage from examination of the alkaloid content of seedlings of *Vinca rosea*, a technique used to gain information about the sequence of alkaloidal transformations. It was found that *Corynanthe*-type systems appeared before detectable amounts of *Aspidosperma* and *Iboga* alkaloids were formed.[41] Direct feeding experiments showed



Scheme 9

[40] It is assumed for the diagram that vincoside has the 3-α configuration. If current work establishes a 3-β configuration for vincoside, then *inversion* at C-3 would be required to generate geissoschizine (41). This would have to occur by a mechanism not involving either loss or transfer of the C-3 proton (see later).

[41] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 948.

that (39) is not significantly incorporated into other alkaloids in mature *Vinca rosea* plants.[41—43] However, [*O-methyl*-^{3}H, *Ar*-^{3}H]geissoschizine was incorporated[44] intact into ajmalicine (1), serpentine [(1), ring C aromatised], akuammicine (2), vindoline (4), and catharanthine (6); further, [*Ar*-$^2H_4$]geissoschizine was incorporated[45] into akuammicine (2) and coronaridine [(6), Δ^{15-20} reduced]. The occurrence of geissoschizine in *Vinca rosea* plants was established by direct isolation.[44,45] These results prove (*a*) biological conversion of the *Corynanthe* system of geissoschizine into the rearranged *Aspidosperma* and *Iboga* skeletons, and (*b*) the rearrangement ($\alpha \rightarrow \beta$) of geissoschizine to generate the *Strychnos* skeleton of akuammicine (2). Interlocking evidence for the $\alpha \rightarrow \beta$ rearrangement came from the incorporation of [*Ar*-^{3}H]vincoside into akuammicine (2).[44] This work is in agreement with ideas[39,46] about the early stages of the rearrangement process.

The findings from experiments with ^{3}H-labelled loganin are collected later but it must be noted here that [2-^{3}H, 2-^{14}C]loganin (10), in which the label corresponds to position 20 of geissoschizine (41), is incorporated into all three types of alkaloids, *e.g.* (1), (4), and (6), with complete loss of ^{3}H. Retention of ^{3}H in any one of these cases would have cast doubt on geissoschizine as a precursor; as it is, additional strength is gained.

Three important compounds were isolated[41,45] from young *Vinca rosea* seedlings *viz.* stemmadenine (43), tabersonine (46), and preakuammicine (42); the first two were known from other sources, the last was new. Chemical correlation of preakuammicine (42) with stemmadenine (43) and akuammicine (2) established its structure, apart from stereochemistry at C-16. The status of the first two as late intermediates on the pathway was established by showing[41] intact incorporation in *Vinca rosea* of [*O-methyl*-^{3}H, 11-^{14}C]stemmadenine into tabersonine (46), vindoline (4), and catharanthine (6). [*O-methyl*-^{3}H, 11-^{14}C]Tabersonine was similarly incorporated into (4) and (6). The latter result has been confirmed[35] by feeding [*Ar*-^{3}H]tabersonine to *Vinca rosea* and isolating radioactive (4) and (6). These results are interpreted[41] in support of the sequence stemmadenine (43) → tabersonine (46) → catharanthine (6). The conversion of tabersonine into catharanthine *in vivo* is interesting and warrants further study. Labelled catharanthine was not converted by the plants into tabersonine.

Stemmadenine (43) may arise in Nature from the pentacyclic *Strychnos* skeleton (42), the latter may be formed from the former, or there may be interconversion by oxidation–reduction. At present there is no rigorous evidence on this point but the timing of stemmadenine's appearance in growing seedlings[41,45] and mechanistic considerations suggest that it follows, or is in

[42] A. R. Battersby, J. C. Byrne, R. S. Kapil, J. A. Martin, T. G. Payne, D. Arigoni, and P. Loew, *Chem. Comm.*, 1968, 951.

[43] Incorporation of activity from corynantheine aldehyde into (4) and (6) occurs in *V. rosea* seedlings[41] but degradations and/or multiple labelling will be necessary before this difference from older plants can be understood.

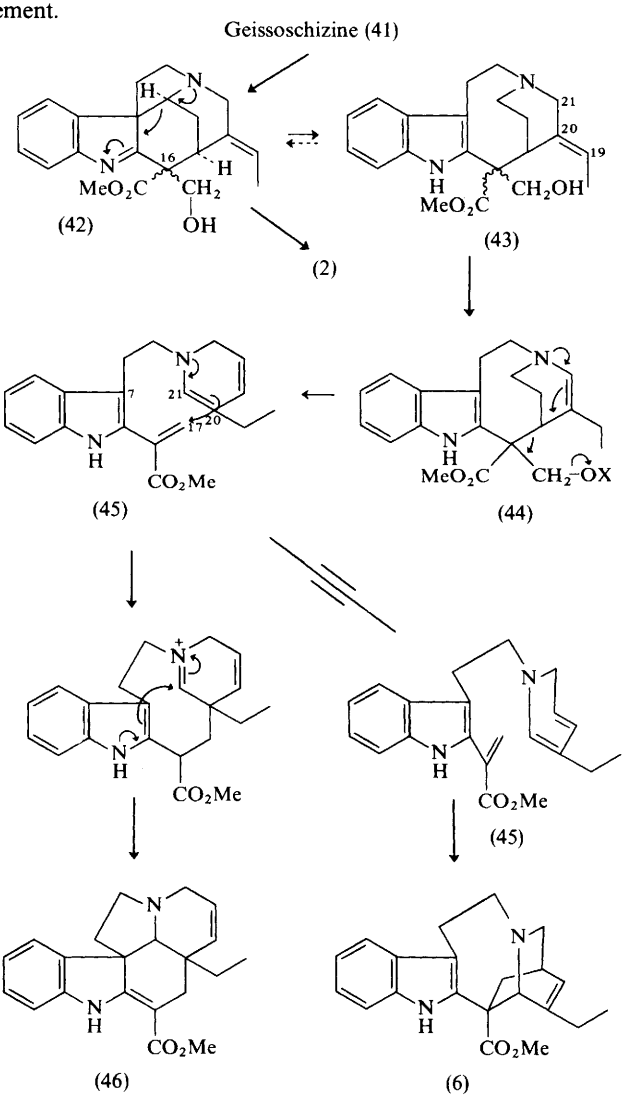
[44] A. R. Battersby and E. S. Hall, *Chem. Comm.*, 1969, 793.

[45] A. I. Scott, P. C. Cherry, and A. A. Qureshi, *J. Amer. Chem. Soc.*, 1969, **91**, 4932.

[46] *cf.* A. R. Battersby, *Chimia*, 1968, **22**, 313.

equilibrium with, the pentacyclic *Strychnos* system. This order is assumed in Scheme 10.

The mechanism by which the *Corynanthe* skeleton is converted into the *Strychnos* system (42) is under current study and there are several chemically reasonable possibilities. The point is left open in Scheme 10 but clearly oxidation is necessary to reach preakuammicine (42) and this might occur before or after rearrangement.



Scheme 10

Having reached stemmadenine (43), the different, and very attractive, mechanism[47] for skeletal fission and new bond formation can be outlined which depends not, as in Scheme 8, on reactions of ketones, but on enamine chemistry (see Scheme 10).

Migration of the $\Delta^{19,20}$ double bond of (43) to give (44), in principle, could allow fragmentation to the acrylic ester (45) which can then ring-close in the two indicated ways leading to tabersonine (46) and catharanthine (6). These two can then be further modified to generate *e.g.* vindoline (4) and coronaridine [(6), $\Delta^{15,20}$ reduced].

The biosynthesis of tabersonine is shown as occurring with 17,20-bond formation before 7,21 largely on the mechanistic grounds evident in Scheme 10; experiments considered to point against such a transannular ring-closure[35,48] can be interpreted in ways not in conflict with Scheme 10.

The illustrated transformations beyond stemmadenine (43) have been reported as occurring also *in vitro* in hot acetic acid[47] but others have not been able to repeat the work.[49]

Returning to the biosynthetic aspects, the incorporation data outlined above from feeding experiments with labelled geissoschizine (41), stemmadenine (43), and tabersonine (46) are in accord with this pathway for the late stages. Further, since the double-bond migration (43) → (44) is an essential step, saturation of it at some earlier stage should block the biosynthesis. In fact, dihydrovincoside [(37), vinyl reduced] gave no significant incorporation into any of the alkaloidal types.[12]

Table *Tracer experiments on* Vinca rosea[12,42]

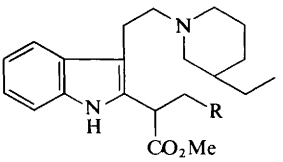
Expt. No.	*Precursor*	*Site of label in loganin*	% *Retention skeletal* ^{3}H			
			Loganin	Cory-nanthe[b]	Aspido-sperma	Iboga
1	[1-$^3H_2$,2-^{14}C]Geraniol	C-1	45	45	47	48
2	[2-^{3}H,2-^{14}C]Geraniol	C-2	95	<5	<5	<5
3	[2-^{3}H,2-^{14}C]Nerol	C-2	101	<5	<5	<5
4[a]	Sodium (3*R*, 4*R*) + (3*S*, 4*S*) [4-$^3H_1$, 2-^{14}C] mevalonate[c]	C-2 and C-7	103	49	52	49
5	Sodium (3*R*, 4*S*) + (3*S*, 4*R*) [4-$^3H_1$, 2-^{14}C] mevalonate[c]	—	10 ± 5	<5	<5	<5
6	[5-^{3}H,*O-methyl*-^{3}H]Loganin	C-5	—	96	99	102

[a] Averaged values from two separate experiments.
[b] Averaged values from three different *Corynanthe* alkaloids.
[c] In each case, only the 3*R*-isomer is biologically effective. Thus expt. 4 tests the 4-*R*-^{3}H label and expt. 5 tests the 4-*S*-^{3}H label.

[47] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 945, 947.
[48] J. P. Kutney, C. Ehret, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, 1968, **90**, 5929.
[49] R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *Chem. Comm.*, 1969, 1475.

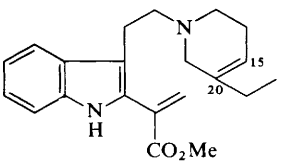
A searching test of the mechanism of these later stages is available from the studies of tritium loss and retention from labelled positions of loganin (10). The Table collects the results and the third column shows the labelling positions(s) in loganin from the precursor used. In connection with Expt. 4, it was established, by using optically pure [5-^{14}C]-(3*R*)-mevalonate, that it is this isomer, not 3*S*, which is the specific precursor of the alkaloids.[42] Results for loganic acid (17) which match those in Expt. 4 for loganin have been obtained in *Swertia carolin-iensis*.[50] The reader should track these labels through Schemes 4 → 6 → 7 → 9 → 10 to confirm the statement that the results are in complete accord with this pathway. In addition, the following conclusions can be drawn: (*a*) the stereo-specificity established for the formation of geraniol double bonds in other biological systems[51] holds in *V. rosea*; (*b*) removal of the C-21 proton during (43) → (44) is stereospecific, and leaves unaffected that derived from C-1 of loganin; (*c*) since ^{3}H at C-2 of loganin is lost in alkaloid formation, ^{3}H at C-7 of loganin, corresponding to C-15 of the *Corynanthe-Strychnos* alkaloids, is retained throughout (Expts. 2 and 4); the configuration at C-7 of loganin is thus stereochemically determining*cf.*[39] for this group; (*d*) ^{3}H at C-5 of loganin appears in the three alkaloidal systems and unambiguous degradation[52] has proved that the alkaloids are labelled solely at the expected site [at C-3 in (1), (4), and (6)]; (*e*) the correspondence of stereochemistry at C-2 of loganin (10) and C-20 of ajmalicine (1) is fortuitous; the loss of ^{3}H from this position is in accord with an extended iminium system (Scheme 9).

Strong support for the formation of (45) in the biological cleavage process came (*a*) from the isolation of tetrahydrosecodine (47) from *Rhazya stricta* and



(47) R = H

(48) R = OH



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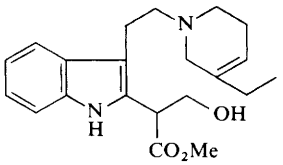

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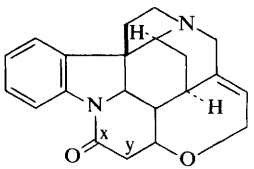
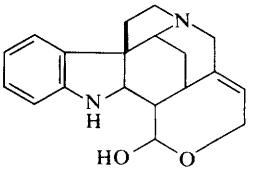


(51)

[50] C. J. Coscia, L. Botta, and R. Guarnaccia, *Arch. Biochem. Biophys.*, 1970, **136**, 498.
[51] G. Popjàk and J. W. Cornforth, *Biochem. J.*, 1966, **101**, 1553.
[52] A. R. Battersby and K. H. Gibson, unpublished work.



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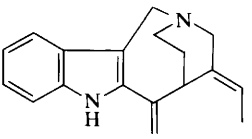


(53)

proof of its presence in *R. orientalis* by dilution analysis;[53] structure (49) is named secodine; and (*b*) by isolation of tetrahydrosecodin-17-ol (48) and the corresponding dihydrobase (50) from *Rhazya orientalis*.[53,54] Closely related bases were also present and other modifications of the secodine system have been found.[55] Further, the presecamines are dimers based upon secodine (49) and its $\Delta^{15,20}$-dihydro derivative.[56] It seems probable that the number of alkaloids based upon the skeleton (49) will grow steadily.

Information on derivatives of the alkaloidal types considered so far is as follows: (*a*) there is good evidence that the biosynthesis of strychnine (51) in *Strychnos nux vomica* plants follows the terpenoid pathway and it is proved that carbons x and y of (51) are derived from acetate; the Wieland–Gumlich aldehyde (52) is not incorporated into strychnine by these plants;[57] (*b*) apparicine (53), which lacks one carbon of the normal tryptamine side chain, is derived from tryptophan with loss of C-2 as shown by comparative feedings to *Aspidosperma pyricollum* of [2-^{14}C, *Ar*-^{3}H]-, and [3-^{14}C, *Ar*-^{3}H]-tryptophan; [*Ar*-^{3}H]stemmadenine (43) is incorporated into apparicine and so loss of the side-chain carbon occurs late in the biosynthesis.[58]

By joining Schemes 4, 6, 7, 9, and 10 together, the marvellous pathway to the indole alkaloids can be seen. The next year or two should see the filling of the now small gaps in the fundamental series of biological transformations. Having largely worked out this route to the three main families, there remain several decades of effort before the vast range of interconnected pathways bringing about further modifications of these basic types is unravelled.

[53] G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Comm.*, 1970, 189; R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *ibid.*, p. 190.
[54] A. R. Battersby and A. K. Bhatnagar, *Chem. Comm.*, 1970, 193.
[55] P. A. Crooks, B. Robinson, and G. F. Smith, *Chem. Comm.*, 1968, 1210; D. A. Evans, G. F. Smith, G. N. Smith, and K. S. J. Stapleford, *Chem. Comm.*, 1968, 859.
[56] G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Comm.*, 1970, 191.
[57] Ch. Schlatter, E. E. Waldner, H. Schmid, W. Maier, and D. Gröger, *Helv. Chim. Acta*, 1969, **52**, 776.
[58] J. P. Kutney, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, 1969, **91**, 4278, 4279.

3

Pyrrolidine, Piperidine, and Pyridine Alkaloids

BY V. A. SNIECKUS

1 Pyrrolidine Alkaloids

This section summarises recent work on alkaloids containing the pyrrolidine nucleus.[1] A short review concerning the synthesis of this group has appeared.[2]

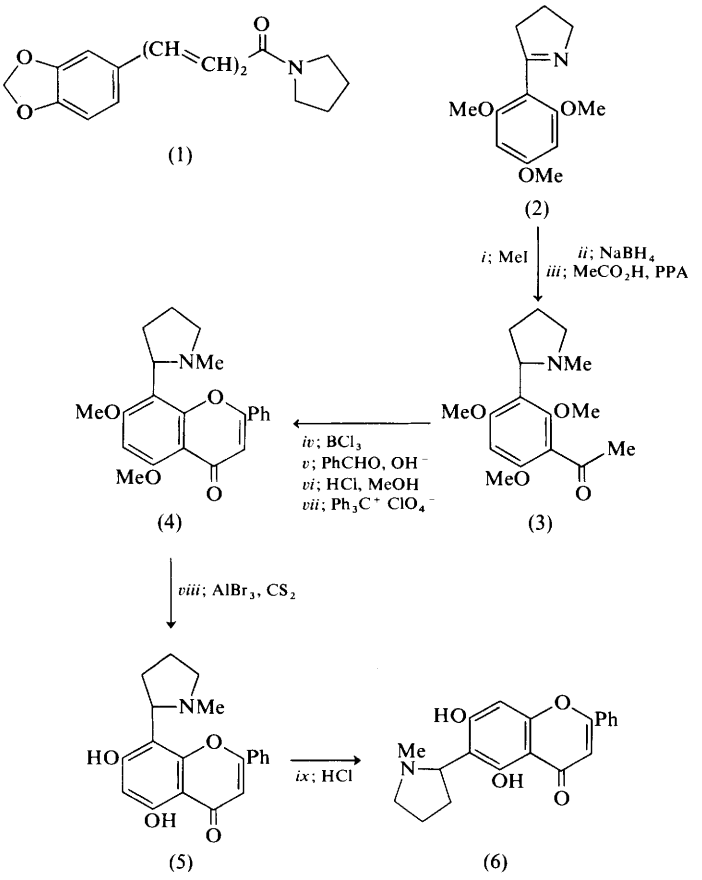
A variety of Labiatae plants have been screened and some of them have been shown to contain pyrrolidine alkaloids.[3] Cuskhygrine has been found in the roots of three *Datura* species[4] and stachydrine has been obtained from *Capparis spinosa*.[5] The structure of trichostachine (1) (*Piper trichostachyon*) has been elucidated by spectral means and confirmed by synthesis.[6] Ficine (5), an interesting flavonoid alkaloid, has been synthesised.[7] Friedel–Crafts reaction between 1,3,5-trimethoxybenzene and 4-aminobutyric acid yielded the pyrrolideine derivative (2). After two unexceptional steps, a second Friedel–Crafts reaction produced the highly substituted aromatic system (3) which was readily converted into the flavone (4) and finally into ficine (5). Interestingly, (5) underwent ready rearrangement to isoficine (6).

2 Piperidine, Pyridine, and some Terpenoid Alkaloids

This section covers alkaloids which have piperidine or pyridine rings as the distinguishing skeletal features, including those which are related to mono- or sesqui-terpenes.

Piperidine and Pyridine Alkaloids.—This group has been reviewed.[8] Separation and identification of nicotine alkaloids has been effected by g.l.c.[9] Other sensitive methods which combine t.l.c. and spectrophotometric analysis have been developed.[10]

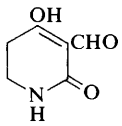
[1] H.-G. Boit, 'Ergebnisse der Alkaloid-Chemie bis 1960,' Akademie-Verlag, Berlin, 1961, p. 50.
[2] W. Nagata, *Yuki Gosei Kagaku Kyokai Shi*, 1968, **26**, 732.
[3] T. P. Pulatova, *Khim. prirod. Soedinenii*, 1969, **5**, 62.
[4] K. Szepczynska, *Diss. Pharm. Pharmacol.*, 1970, **22**, 35; (*Chem. Abs.*, 1970, **73**, 939v).
[5] S. Mukhamedova, S. T. Akramov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 67.
[6] J. Singh, K. L. Dhar, and C. K. Atal, *Tetrahedron Letters*, 1969, 4975.
[7] B. Anjaneyulu and T. R. Govindachari, *Tetrahedron Letters*, 1969, 2847.
[8] W. A. Ayer and T. E. Habgood in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, vol. XI, 1968, p. 459.
[9] W. W. Weeks, D. L. Davis, and L. P. Bush, *J. Chromatog.*, 1969, **43**, 506.
[10] E. Sisler, *Analyt. Biochem.*, 1969, **31**, 183; K. Blaim and R. Ciszewska, *Chem. analit.*, 1968, **13**, 1295; M. Ya. Lovkova and N. S. Monozhedinova, *Priklad. Biokhim. i Mikrobiol.*, 1969, **5**, 487; H.-P. Harke, B. Frahm, and C. Schultz, *Z. analyt. Chem.*, 1969, **244**, 119.



Alkaloids have been isolated from the following sources: *Adenocarpus manii*,[11] areca nut (supari),[12] *Carica papaya*,[13] *Genista hystrix*,[14] *Gentiana olgae*,[15] which contains gentianaine (7), *G. olivieri*,[15] *G. turkestonarum*,[15] *G. kauffmanniana*,[15] *Nauclea diderichi*,[16] *L. Priestleya elliptica*,[17] *Pinus jeffreyi*,[18] *P. resinosa*,[18] *P. nigra*,[18] *Streptomyces* strains,[19] which have yielded nigrifactine (8), and

[11] R. Bernasconi and E. Steinegger, *Pharm. Acta Helv.*, 1970, **45**, 42.
[12] S. N. Mitra, B. R. Roy, and H. Das, *J. Inst. Chemists (India)*, 1969, **41**, 154.
[13] T. M. Smalberger, G. J. H. Rall, and H. L. DeWaal, *Tydskr. Natuurwetensk.*, 1969, **8**, 156.
[14] E. Steinegger and F. Schnyder, *Pharm. Acta Helv.*, 1970, **45**, 157.
[15] T. U. Rakhmatullaev, S. T. Akramov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 32.
[16] S. McLean and D. G. Murray, *Canad. J. Chem.*, 1970, **48**, 867.
[17] E. Schlunegger and E. Steinegger, *Pharm. Acta Helv.*, 1970, **45**, 147.
[18] M. Siegel, *Biol. Zentralbl.*, 1969, **88**, 629.
[19] T. Terashima, Y. Kuroda, and Y. Kaneko, *Tetrahedron Letters*, 1969, 2535.

Vandopsis longicaulis.[20] Certain tumour-inhibitory plants of the Piperaceae and Rhizophoraceae families have yielded amides, *e.g.* $\Delta^{\alpha,\beta}$-dihydropiperine (9) occurs in *Piper novae-hollandiae* Miq.[21] Macrocyclic alkaloids, *e.g.* azimine (10), have been fully defined.[22] Further evidence for the nature of *Lythrum* bases has been obtained by synthesis of the overall skeleton.[23] The key step in the synthesis involved formation of the 17-membered ring (11) → (12). Directions for the isolation and degradation of piperine (9, with γ,δ-double bond) have been included in a unique laboratory text.[24]



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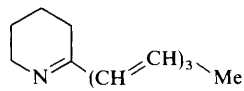

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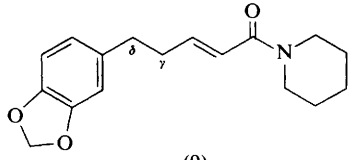

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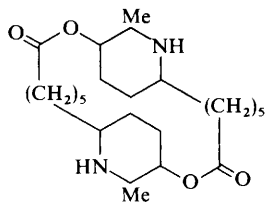

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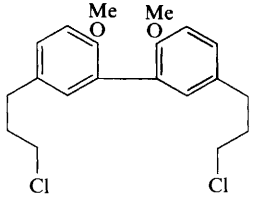

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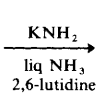
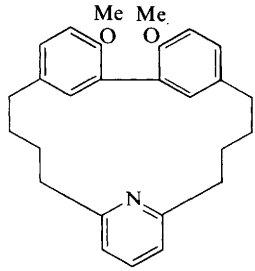
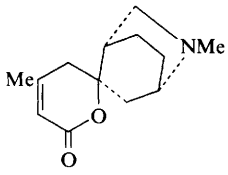




(12)



(13)

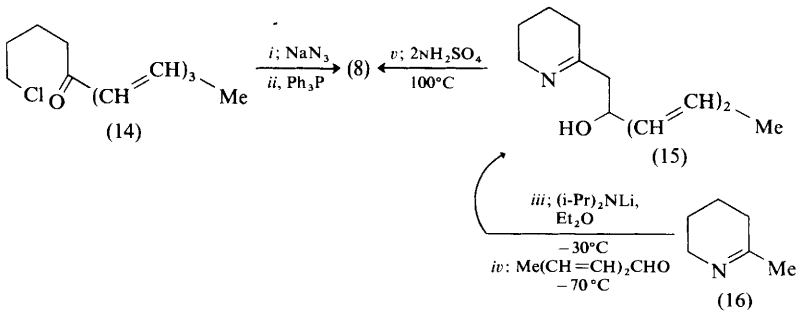
The technique of chemical ionisation mass spectrometry has shown promise in the structural elucidation of nicotine alkaloids.[25] The absolute configurations of a number of simple piperidine alkaloids have been determined by o.r.d. and

[20] S. Brandänge and B. Lüning, *Acta Chem. Scand.*, 1970, **24**, 353.
[21] T. R. Govindachari, S. J. Jadhav, B. S. Joshi, V. N. Kamat, P. A. Mohamed, P. C. Parthasarathy, S. J. Patankar, D. Prakash, D. F. Rane, and N. Viswanathan, *Indian J. Chem.*, 1969, **7**, 308; J. W. Loder, A. Moorhouse, and G. B. Russell, *Austral. J. Chem.*, 1969, **22**, 1531; J. W. Loder and G. B. Russell, *Austral. J. Chem.*, 1969, **22**, 1271.
[22] T. M. Smalberger, G. J. H. Rall, H. L. De Waal, and R. R. Arndt, *Tetrahedron*, 1968, **24**, 6417.
[23] E. Fujita, K. Fuji, and K. Tanaka, *Tetrahedron Letters*, 1968, 5905.
[24] R. Ikan, 'Natural Products,' Academic Press, New York, 1969, p. 185.
[25] H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Amer. Chem. Soc.*, 1970, **92**, 1590.

c.d. studies: (−)-nipecotinic acid,[26] halosaline,[27] conhydrine,[28] anaferine,[29] and sedridine.[30] The absolute configuration of dioscorine (13) has been established.[31]

The subject of total synthesis of piperidine alkaloids has been briefly reviewed.[32] Simple syntheses of the optical isomers of sedrinine have been described.[33]

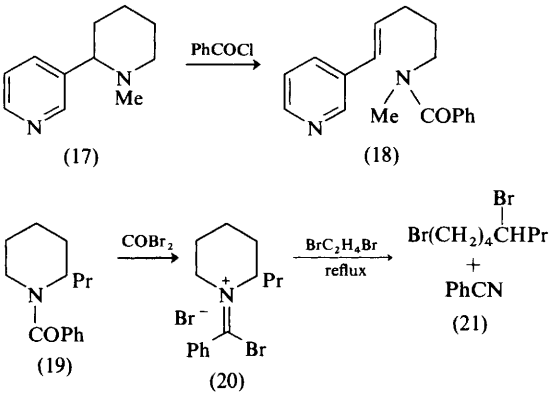
Two interesting syntheses of the unstable piperidine alkaloid, nigrifactine (8), have been developed. In one report,[34] the highly unsaturated ketone (14), prepared by conventional means, was converted into (8) *via* an unusual reaction which may involve a phosphine-imine intermediate; in the other route,[35] elaboration of the side chain (16) → (15) was achieved by a condensation which takes advantage of the acidic methyl protons in (16). 1,4-Dihydro-1-methyl-4-oxonicotinonitrile and pelletierine specifically labelled with ^{14}C have been prepared.[36]



A dimerisation reaction of *N*-methylanabasine (17) has been reported[37] and a modification of the useful dealkylation reaction for tertiary amines[38] has been used in a partial degradation (17) → (18).[39] The harsh conditions necessary for the von Braun reaction of heterocyclic benzamides with phosphorous pentabromide has generally precluded its application to structural determination. It has now been found that carbonyl bromide is a useful reagent for this reaction

[26] H. Ripperger and K. Schreiber, *Chem. Ber.*, 1969, **102**, 2864.
[27] K. H. Michel, F. Sandberg, F. Haglid, T. Norin, R. P. K. Chan, and J. Cymerman Craig, *Acta Chem. Scand.*, 1969, **23**, 3479.
[28] G. Fodor, E. Banerschmidt, and J. Cymerman Craig, *Canad. J. Chem.*, 1969, **47**, 4393.
[29] M. M. El-Olemy and A. E. Schwarting, *J. Org. Chem.*, 1969, **34**, 1352.
[30] H. C. Beyerman, L. Maat, J. P. Visser, J. Cymerman Craig, R. P. K. Chan, and S. K. Roy, *Rec. Trav. chim.*, 1969, **88**, 1012.
[31] A. F. Beecham, H. H. Mills, F. B. Wilson, C. B. Page, and A. R. Pinder, *Tetrahedron Letters*, 1969, 3745.
[32] W. Nagata, *Yuki Gosei Kagaku Kyokai Shi*, 1968, **26**, 732.
[33] C. Schoepf, E. Gams, F. Koppernock, R. Rausch, and R. Walbe, *Annalen*, 1970, **732**, 181.
[34] M. Pailer and E. Haslinger, *Monatsh.*, 1970, **101**, 508.
[35] H. W. Gschwend, *Tetrahedron Letters*, 1970, 2711.
[36] H. E. Johnson and G. R. Waller, *J. Labelled Compounds*, 1968, **4**, 295; R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1969, **47**, 445.
[37] A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, and G. A. Tolkacheva, *Khim. geterotsikl. Soedinenii.*, 1969, 364.
[38] J. D. Hobson and J. G. McCluskey, *J. Chem. Soc.* (*C*), 1967, 2015.
[39] Ya. L. Gol'dfarb, R. M. Ispiryan, and L. I. Belenkii, *Izvest. Akad. Nauk. SSSR, Ser. khim.*, 1969, 923.

(19) → (21).[40] In fact, it was possible to characterise the intermediate iminium bromide (20) and convert it into the crystalline hexafluoroantimonate salt.

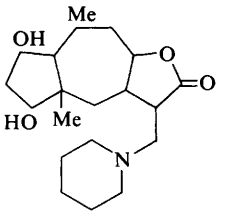


Mono- and Sesqui-terpenoid Alkaloids.—Excellent comprehensive reviews on the mono-[41] and sesqui-terpenoid[42] alkaloids have appeared. Reviews on specific groups of monoterpenoid alkaloids (Gentianaceae,[43] *Skytanthus acutus*[44]) are less readily accessible.

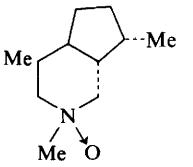
Possibly as a result of their importance in indole alkaloid biosynthesis, a great deal of attention has been focused on the monoterpenoid group. Recent investigations of plant species which have yielded these alkaloids include: *Alstonia venenata*,[45] *Dipsacus azureus*,[46] *Erythraea* species,[47] *Gaillardia pulchella* Foug.[48] (22), various *Gentiana* species,[47,49] *Jasminum* species,[50] *Menyanthes trifoliata* L.,[51] *Pedicularis olgae*,[52,53] *P. rhinantoides*,[52b] *Plantago indica* (*P.*

[40] G. Fodor, J. J. Ryan, and F. Letourneau, *J. Amer. Chem. Soc.*, 1969, **91**, 7768.
[41] W. C. Wildman, J. Le Men, and K. Wiesner in 'Cyclopentanoid Terpene Derivatives,' eds. W. I. Taylor and A. R. Battersby, Marcel Dekker, Inc., New York, 1969, p. 239.
[42] O. E. Edwards in 'Cyclopentanoid Terpene Derivatives,' eds. W. I. Taylor and A. R. Battersby, Marcel Dekker, Inc., New York, 1969, p. 357; see also J. T. Wrobel in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1967, vol. IX, p. 441.
[43] N. Marekov and S. Popov, *Farmatsiya (Sofia)*, 1969, **19**, 32.
[44] G. B. Marini-Bettolo, *Ann. Ist. Super. Sanita*, 1968, **4**, 489.
[45] A. B. Ray and A. Chatterjee, *Tetrahedron Letters*, 1968, 2763.
[46] T. U. Rakhmatullaev, S. T. Akramov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii.*, 1969, **5**, 64.
[47] N. Marekov, *Izvest. Otdel. Khim. Nauk, Bulg. Akad. Nauk*, 1970, **2**, 575.
[48] M. Yanagita, S. Inayama, T. Kawamata, and T. Okura, *Tetrahedron Letters*, 1969, 2073.
[49] N. Marev and M. Arnaudov, *Doklady Bolgar. Akad. Nauk*, 1970, **23**, 81; *Chem. Abs.*, 1970, **73**, 970y; S. T. Akramov, M. R. Yagudaev, T. U. Rakhmatullaev, A. Samatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii.*, 1969, **5**, 14.
[50] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1969, **22**, 1283.
[51] F. Rulko, *Roczniki Chem.*, 1969, **43**, 1831.
[52] [a] A. Abdusamatov, S. Khadimdzhanov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii.*, 1969, **5**, 457; [b] A. Abdusamatov and S. Yu. Yunusov, *ibid.*, 1969, **5**, 334.
[53] K. Torssell, *Acta Chem. Scand.*, 1968, **22**, 2715.

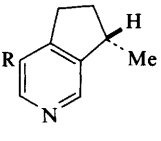
ramosa),[53] *Swertia graciliflora*,[46] *S. marginata*,[46] *Skytanthus acutus*[54] (23), and *Tecoma stans*.[41,55]



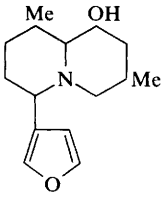
(22)



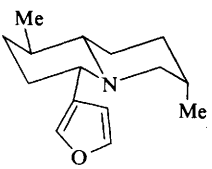
(23)



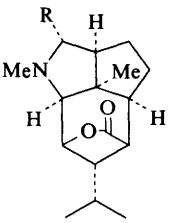
(24)



(25)



(26)



(27)

Plantagonine has been reassigned[53] structure (24; R = CO_2H), as predicted from the available physical data.[41] It was also obtained by oxidation of indicaine (24; R = CHO) which co-occurs with plantagonine in the same plant species. The total synthesis of the enantiomer of tecostidine (24; R = CH_2OH) which was reviewed earlier[41] has been described in detail.[56]

The Hofmann reaction of various stereoisomers of skytanthine methiodides has been studied directly in the gas chromatograph.[57] The conformational differences are important in determining the direction and extent of β-elimination, as opposed to regeneration of the tertiary amines. A mass spectral study of one *Gentiana* alkaloid has been reported.[58]

Nupharolidine (25), a new sesquiterpene alkaloid, has been isolated from *Nuphar luteum* and characterised mainly by spectral means.[59] The *Dendrobium* species (Orchidaceae) is known to be rich in sesquiterpene alkaloids. A taxonomic survey of Australian Orchidaceae which includes a discussion of *Dendrobium* has appeared.[60]

[54] M. P. Streeter, G. Adolphen, and H. H. Appel, *Chem. and Ind.*, 1969, 1631.
[55] E. M. Dickinson and G. Jones, *Tetrahedron*, 1969, **25**, 1523.
[56] G. W. K. Cavill and A Zeitlin, *Bull. Nat. Inst. Sci. India*, 1968, No. 37, 100; *Austral. J. Chem.*, 1967, **20**, 349.
[57] E. J. Eisenbraun, H. Auda, K. S. Shorno, G. R. Waller, and H. H. Appel, *J. Org. Chem.*, 1970, **35**, 1364.
[58] S. T. Akramov, A. Samatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii.*, 1969, **5**, 66.
[59] J. T. Wrobel and A. Iwanow, *Roczniki Chem.*, 1969, **43**, 997.
[60] L. J. Lawler and M. Slaytor, *Phytochemistry*, 1969, **8**, 1959.

Firm evidence for the absolute configuration of (−)-deoxynupharidine (26) has been obtained.[61] The enantiomeric structure had been previously proposed on the basis of formation of optically active methylsuccinic acid from the ozonolysis of a Hofmann degradation product. The ambiguity in this assignment was noted and the absolute configuration was established by correlation with *R*-(−)-α-methyladipic acid which was prepared in two steps from *R*-(+)-3-methylcyclohexanone. Thus the earlier assignment[42] is incorrect. Dendrine (27; R = CH_2CO_2Me) has been synthesised by treatment of dendrobine (27, R = H) with *N*-bromosuccinimide followed by a Reformatsky-type reaction.[62]

[61] C. F. Wong, E. Auer, and R. T. Lalonde, *J. Org. Chem.*, 1970, **35**, 517.
[62] I. Granelli and K. Leander, *Acta Chem. Scand.*, 1970, **24**, 1108.

4

Tropane Alkaloids

BY J. E. SAXTON

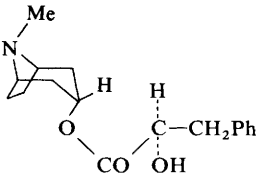
There has been comparatively little activity in this group of alkaloids during the period under review. The pharmacological and clinical importance of some of these alkaloids has stimulated further attempts to devise new or improved methods of quantitative assay of alkaloid mixtures, *e.g.* by gas–liquid chromatography,[1,2] and by fluorimetric[3] or densitometric[4] methods. The t.l.c. behaviour of many of these alkaloids has also been examined.[5] An Indian group has conducted a search for an improved source of hyoscyamine and hyoscine in several Solanaceous plants indigenous to the Indian subcontinent,[6] while other investigators have attempted to increase the yield of belladonna alkaloids obtained in extraction procedures.[7,8] Finally, the influence of gibberellic acid on the growth and alkaloid content in *Datura innoxia* has also been studied.[9]

A few new alkaloids have been isolated during investigations on Australasian plants. The major alkaloid of two Australian shrubs, *Anthocercis viscosa* R. Br. and *A. fasciculata* F. Muell. (fam. Solanaceae), has been identified as (−)-hyoscyamine.[10] The same base (partly racemic) is one of the seven alkaloidal constituents of *A. littorea* Labill.; another is meteloidine. The major alkaloid, however, is littorine, which has been identified as *R*-(−)-3α-(2-hydroxy-3-phenylpropionyloxy)tropane (1). The isolation of tropane alkaloids from the *Anthocercis* species justifies the inclusion of this genus in the Solanaceae; previously it had been included in the Scrophulariaceae but had recently been transferred to the Solanaceae on botanical grounds.[10] Recently, littorine has also been isolated from *Datura sanguinea* R. and P.[11]

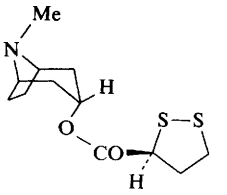
[1] R. O. Zimmerer and L. T. Grady, *J. Pharm. Sci.*, 1970, **59**, 87.
[2] M. J. Solomon, F. A. Crane, B. L. Wu Chu, and E. S. Mika, *J. Pharm. Sci.*, 1969, **58**, 264.
[3] L. A. Roberts, *J. Pharm. Sci.*, 1969, **58**, 1015.
[4] M. S. Shipalov, V. E. Chichiro, and Z. P. Kostennikova, *Priklad. Biochim. i Mikrobiol.*, 1969, **5**, 502.
[5] G. L. Szendey, *Z. analyt. chem.*, 1969, **244**, 257.
[6] B. K. Moza, D. K. Basu, and U. P. Basu, *Indian J. Chem.*, 1969, **7**, 414.
[7] A. Puech, M. Jacob, and J. J. Serrano, *Ann. pharm. franç.*, 1969, **27**, 201.
[8] J. Helman, *J. Pharm. Sci.*, 1969, **58**, 1085.
[9] A. S. Sinha and L. C. Varma, *Indian J. Pharm.*, 1970, **32**, 40.
[10] J. R. Cannon, K. R. Joshi, G. V. Meehan, and J. R. Williams, *Austral. J. Chem.*, 1969, **22**, 221.
[11] W. C. Evans and V. A. Major, *J. Chem. Soc.* (*C*), 1968, 2775.

Another new alkaloid in this series is tropine 3,4,5-trimethoxycinnamate, which occurs in the stem bark of *Erythroxylum ellipticum* R. Br. (fam. Erythroxylaceae), a large tree indigenous to Queensland.[12]

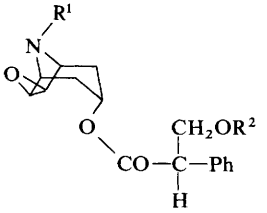
Several esters of tropine have also been found in *Bruguiera sexangula* (Lour.) Poir. (fam. Rhizophoraceae), a tropical mangrove found in New Guinea, and the related Australian species, *B. exaristata* Ding Hou.[13,14] These esters include the acetate, propionate, isobutyrate, butyrate, isovalerate or α-methylbutyrate (not differentiated), the benzoate, and the 1,2-dithiolan-3-carboxylate (brugine).[14] The propionate and butyrate, and brugine had not previously been encountered from natural sources. The structure and absolute configuration of brugine (2) have recently been confirmed by its synthesis from tropine and 1,2-dithiolan-3-carboxylic acid.[15]



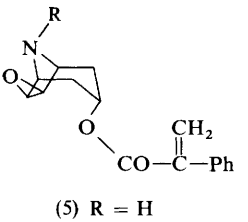
(1)



(2)



(3) R^1 = Me, R^2 = Ac
(4) R^1 = R^2 = H



(5) R = H
(6) R = CHO

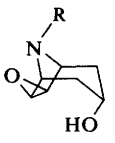
The oxidation of *O*-acetylscopolamine (3) by means of aqueous potassium permanganate[16,17] has been reinvestigated.[18] The major product, after acid hydrolysis, is nor(−)-scopolamine (4), but from the mother liquors two further products were obtained. These were identified as aponorscopolamine (5) and its *N*-formyl derivative (6). Oxidation of (−)-scopolamine itself by means of

[12] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1970, **23**, 421.
[13] J. W. Loder and G. B. Russell, *Austral. J. Chem.*, 1969, **22**, 1271.
[14] J. W. Loder and G. B. Russell, *Tetrahedron Letters*, 1966, 6327; A. F. Beecham, J. W. Loder, and G. B. Russell, *Tetrahedron Letters*, 1968, 1785.
[15] G. Claeson, private communication reported in ref. 13.
[16] H. L. Schmidt, G. Werner, and G. Kumpe, *Annalen*, 1965, **688**, 228.
[17] H. Bertholdt and R. Pfleger, *Arch. Pharm.*, 1968, **301**, 934.
[18] G. Werner and R. Schickfluss, *Annalen*, 1969, **729**, 152.

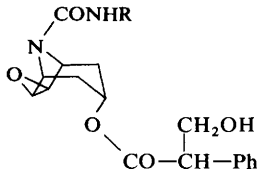
potassium permanganate gives directly a higher yield of norscopolamine, particularly if a saponification stage is introduced to hydrolyse the *N*-formyl derivative which is also produced.[18] Surprisingly, the primary alcohol function remains untouched; this lack of reactivity is attributed to the presence of a strong hydrogen bond between the hydroxy-group and the epoxide group.[18]

Some new derivatives of norscopine (7), scopine (8), and nor(−)-scopolamine (4) have been prepared[18,19] for pharmacological evaluation. Derivatives of nor(−)-scopolamine include *N*-alkyl derivatives from reaction with alkyl halides, polymethylene halides, or epoxides; substituted ureas (9) from the reaction with alkyl isocyanates, and urethanes (10) from (−)-scopolamine and alkyl isocyanates.[19]

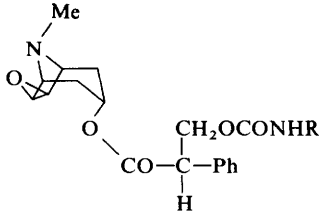
The value of chemical ionisation mass spectrometry as a complementary technique to conventional electron impact mass spectrometry has been illustrated by Fales *et al.*,[20] who investigated the behaviour of representatives of nine of the major alkaloid families, including homatropine. In C.I. mass spectrometry the quasi-molecular ion [QM^+, *i.e.* $(M + 1)^+$] is invariably more abundant than is the molecular ion in E.I. mass spectrometry. Thus, with methane as reactant gas, homatropine shows a moderately strong quasi-molecular ion, and an ion at *m/e* 258 owing to $QM^+ - H_2O$. In the E.I. mass spectrum, homatropine shows a very small molecular ion, and no ion at *m/e* 258; thus the presence of a hydroxy-group passes unnoticed.[20]



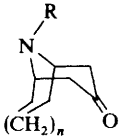
(7) R = H
(8) R = Me



(9)



(10)



(11) R = Me, $n = 1$
(12) R = CHO, $n = 1$
(13) R = Me, $n = 0$
(14) R = CHO, $n = 0$

The photolysis of pseudopelletierine (11) in benzene solution saturated with oxygen affords the corresponding *N*-formyl compound (12) in moderate yield

[19] G. Werner and R. Schickfluss, *Annalen*, 1970, **731**, 1.
[20] H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Amer. Chem. Soc.*, 1970, **92**, 1590.

(55—60%);[21] the analogous photolysis of tropinone (13) gives the lower homologue (14) in 40—50% yield. This procedure accordingly provides an alternative to the older oxidation method by means of chromium trioxide in pyridine, which gives comparable yields.

The mechanism of the photolytic oxidation is at present unknown. That photochemically-generated singlet oxygen is involved is suggested by the fact that the oxidation may be effected when light is absorbed by sensitizers, and the reaction may be quenched by the addition of singlet-oxygen scavengers. However, neither singlet oxygen alone nor ground-state oxygen in the presence of radical initiators converts the *N*-methyl group into an *N*-formyl group. It is suggested that the carbonyl group in the reactant molecule acts as sensitizer in direct photolysis, and its excited state is quenched by dissolved oxygen. In this way singlet oxygen is generated adjacent to the *N*-methyl group, and oxidation ensues, possibly *via* an α-hydroperoxide, which could lose the elements of water to give the observed product.[21]

[21] M. H. Fisch, J. C. Gramain, and J. C. Oleson, *Chem. Comm.*, 1970, 13.

5

The Pyrrolizidine Alkaloids

BY J. E. SAXTON

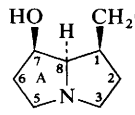
1 Structure, Stereochemistry, and Reactions of the Necines

The structure and stereochemistry of the saturated pyrrolizidinediols have been studied by Culvenor and his collaborators.[1] The structures of the readily available isomers platynecine (1) and dihydroxyheliotridane (2) have been thoroughly established earlier, but hitherto the remaining diols obtained by hydrolysis of alkaloids have been too inaccessible for detailed study. These include hastanecine from the alkaloid hastacine, turneforcidine from turneforcine, macronecine from macrophylline, and an unnamed amino-alcohol from retusine.

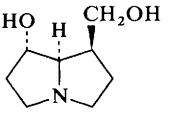
A comparison of the mass spectra of platynecine, dihydroxyheliotridane, hastanecine, and the aminoalcohol from retusine immediately confirms that these compounds are stereoisomers, since the spectra are closely similar and each one exhibits a base peak at *m/e* 82, with only one other major ion, at *m/e* 113. In these compounds the C(7)–C(8) bond is the most labile, and fragmentation occurs to give the ions (3) and (4); the main features of the spectrum are thus determined by the 7-hydroxy-group. In contrast, when ring A is unsubstituted, as in trachelanthamidine (5), the dominant fission is at the C(1)–C(8) bond, with formation of an ion (6) at *m/e* 83. This ion is responsible for the base peak in the spectrum, and loses a hydrogen atom to give a less intense peak at *m/e* 82. Macronecine exhibits a base peak at *m/e* 83, and accordingly appears to have an unsubstituted ring A. Since it is not a carbinolamine the second hydroxy-group must be at C-1 or C-2. That it is at C-2 is indicated by the close similarity of the mass spectra of macronecine and the 2-hydroxy-1-hydroxymethylpyrrolizidine of undefined stereochemistry, prepared by the method of Adams *et al.*;[2] the resemblance to the mass spectrum of 1β-hydroxy-1α-hydroxymethyl-8α-pyrrolizidine is less striking. This conclusion is verified by the n.m.r. spectrum of macronecine, which exhibits a multiplet at τ5.80, appropriate to a C*H*OH grouping, thus establishing the location of the second hydroxy-group at C-2. Since macronecine is a 1β-hydroxymethyl-8β-pyrrolizidine derivative (by virtue

[1] A. J. Aasen, C. C. J. Culvenor, and L. W. Smith, *J. Org. Chem.*, 1969, **34**, 4137.
[2] R. Adams, S. Miyano, and M. D. Nair, *J. Amer. Chem. Soc.*, 1961, **83**, 3323.

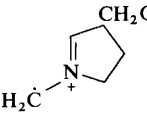
of the degradation of the macronecine-ester alkaloid macrophylline to laburnine[3]) it must be 2-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine, and the n.m.r. coupling constants are in best agreement with a 2β-hydroxy-group (7).



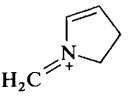
Platynecine (1)



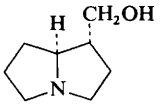
Dihydroxyheliotridane (2)



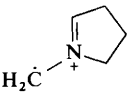
(3)



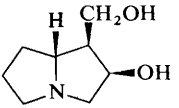
(4)



Trachelanthamidine (5)

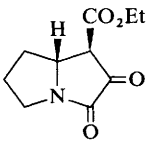


(6)

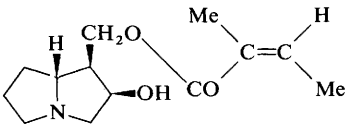


Macronecine (7)

This conclusion has been confirmed by a total synthesis of macronecine (7), which involves successive reductions of the racemic pyrrolizidine ester (8) by zinc and acetic acid, followed by lithium aluminium hydride.[4] Resolution was achieved *via* the α-bromo-D-camphor-π-sulphonate salts. The conclusion concerning the relative stereochemistry in macronecine was substantiated by the preparation of the other three racemates having the same gross structure as macronecine, and a detailed comparison of their n.m.r. spectra.[4] In consequence of this work, the complete structure of macrophylline is as given in (9).[4]



(8)



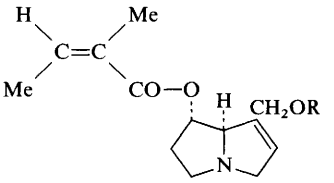
Macrophylline (9)

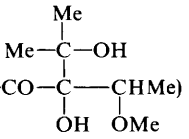
Since it proved impossible to deduce the stereochemistry of hastanecine and the aminoalcohol from retusine, by analysis of the n.m.r. spectra of these diols and the parent alkaloids, an independent chemical correlation with a diol of known configuration was attempted.[1] The starting material selected was 7-angeloylheliotridine (11), prepared by the periodate oxidation of lasiocarpine (10). Hydrogenation of (11) gave the 1β-hydroxymethyl isomer (12), since it afforded dihydroxyheliotridane (2) on hydrolysis. Jones oxidation of (12) gave the corresponding carboxylic acid, the ethyl ester of which epimerised at C-1 and also suffered transesterification when treated with sodium methoxide, to give 1α-methoxycarbonyl-7α-hydroxy-8α-pyrrolizidine (13). Reduction of (13)

[3] A. V. Danilova and L. M. Utkin, *Zhur. obshchei. Khim.*, 1960, **30**, 345 (*Chem. Abs.*, 1960, **54**, 22698).

[4] A. J. Aasen and C. C. J. Culvenor, *J. Org. Chem.*, 1969, **34**, 4143.

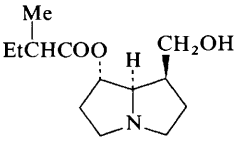
by lithium aluminium hydride finally afforded the corresponding diol (14), which was shown conclusively to be the enantiomer of hastanecine(15).[1]



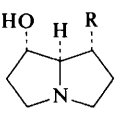


Lasiocarpine (10; R = —CO—C(OH)(Me)—CHMe(OMe))

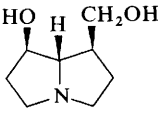
7-Angeloylheliotridine (11; R = H)



(12)



(13; R = CO_2Me)
(14; R = CH_2OH)

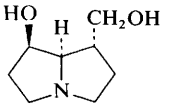


Hastanecine (15)

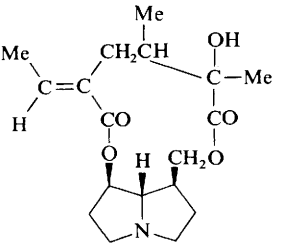
A necessary corollary of this conclusion is that the aminoalcohol from retusine must have the *relative* configuration shown in (16). This was confirmed when it was shown by direct comparison that the aminoalcohol from retusine is enantiomeric with 7α-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine. Thus the absolute configuration of this aminoalcohol is also as given in (16). A comparison of the physical constants of (16) and those of turneforcidine also suggests the possible identity of these diols; however, a discrepancy in the optical rotation data and the lack of a retusine-derived specimen rendered an independent proof necessary. This was achieved[5] by Jones oxidation of the hydroxypyrrolizidine ester (13) to the corresponding ketone, which on catalytic reduction afforded the epimeric hydroxyester (17). Reduction of (17) by lithium aluminium hydride gave the corresponding primary alcohol (16), which was shown to be identical with that from retusine. Since this compound has the same optical rotation as that described for turneforcidine, it is concluded that the previously reported value for the retusine-derived diol was in error, and the identity of this diol with turneforcidine is now regarded as established.[5]

The complete structures of hastacine and retusine can now be depicted as (18) and (19) respectively.

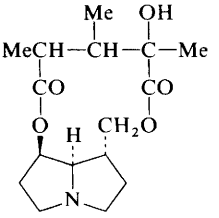
[5] A. J. Aasen and C. C. J. Culvenor, *Austral. J. Chem.*, 1969, **22**, 2657.



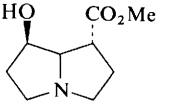
Turniforcidine (16)



Hastacine (18)

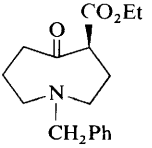


Retusine (19)

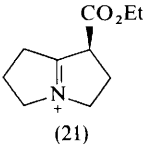


(17)

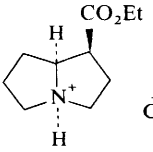
A new, stereospecific synthesis of (±)-isoretronecanol, by a transannular route, has been developed by Leonard *et al.*[6] Dieckmann cyclisation of *NN*-bis-(γ-ethoxycarbonylpropyl)benzylamine gave ethyl 1-benzyl-5-oxo-1-azacyclo-octane-4-carboxylate (20), whose perchlorate was shown to possess a bicyclic structure. Hydrogenation of this perchlorate in ethanol, using palladised charcoal catalyst, afforded ethyl (±)-isoretronecanolate perchlorate (22) as sole product, presumably by stereospecific addition of hydrogen at the less hindered face of the intermediate debenzylated immonium ion (21). Reduction of the free base corresponding to (22), by means of lithium aluminium hydride, gave (±)-isoretronecanol (23), the stereochemical purity of which was shown by g.l.c. analysis to be >98%.



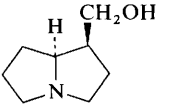
(20)



(21)



(22)

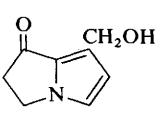


(−)-Isoretronecanol (23)

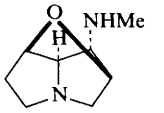
[6] N. J. Leonard and T. Sato, *J. Org. Chem.*, 1969, **34**, 1066.

2 Simple Pyrrolizidine Alkaloids

The flowers of *Urechites karwinsky* Mueller (Apocynaceae) are widely used as a condiment in Salvador, while the roots are highly toxic and are used for killing small animals. A positive test for alkaloids was given only by the roots, which on extraction afforded three alkaloids.[7] Two of these were obtained in very small quantity only, and have not yet been further studied. The major alkaloid loroquine (24), $C_8H_9NO_2$, m.p. 77—78 °C, is a stable derivative of dihydropyrrolizine. The spectrographic evidence, and in particular the n.m.r. spectrum, is diagnostic for the structure (24), which was firmly established by reduction with sodium borohydride to the corresponding diol, and oxidation by means of manganese dioxide to the corresponding keto-aldehyde. The physical properties of both these products were identical with those reported by Culvenor *et al.*[8] for authentic samples prepared independently.



Loroquine (24)



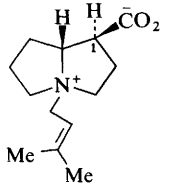
Loline = Festucine (25)

The structure (25) has been deduced for both loline, an alkaloid of *Lolium cuneatum* Nevski,[9,10] and festucine, a constituent of *Festuca arundinacea* Schreb.[11,12] The identity of loline and festucine has now been confirmed by direct comparison.[13]

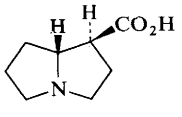
Two further quaternary pyrrolizidine alkaloids have been isolated by Sasaki and Hirata[14] from *Anodendron affine* Druce. These are anodendrine (26) and its C-1 epimer alloanodendrine. In confirmation of these structures, anodendrine gave (+)-laburninic acid (27) on palladium-catalysed hydrogenolysis, whereas alloanodendrine gave (+)-isoretronecanolic acid, the C-1 epimer of (27). The structures of both zwitterionic alkaloids were then finally established by synthesis.[14]

Details of the *X*-ray determination of the structure of cassipourine (28), the alkaloid of *Cassipourea gummiflua* Tul. var *verticellata* Lewis,[15] have now been

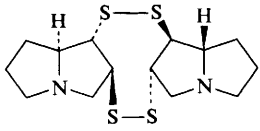
[7] J. Borges del Castillo, A. G. Espana de Aguirre, J. L. Bretón, A. G. González, and J. Trujillo, *Tetrahedron Letters*, 1970, 1219.
[8] C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Tetrahedron Letters*, 1969, 3599.
[9] S. Y. Yunusov and S. T. Akramov, *Zhur. Obshchei Khim.*, 1960, **30**, 3132 (*Chem. Abs.*, 1961, **55**, 19981).
[10] S. T. Akramov and S. Y. Yunusov, *Khim. prirod. Soedinenii.*, 1965, **4**, 262 (*Chem. Abs.*, 1966, **64**, 5152).
[11] S. G. Yates and H. L. Tookey, *Austral. J. Chem.*, 1965, **18**, 53.
[12] J. A. McMillan and R. E. Dickerson, unpublished work, quoted in ref. 11.
[13] A. J. Aasen and C. C. J. Culvenor, *Austral. J. Chem.*, 1969, **22**, 2021.
[14] K. Sasaki and Y. Hirata, *Tetrahedron Letters*, 1969, 4065; *Tetrahedron*, 1970, **26**, 2119.
[15] R. G. Cooks, F. L. Warren, and D. H. Williams, *J. Chem. Soc.* (*C*), 1967, 286.



Anodendrine (26)



(27)



Cassipourine (28)

published.[16] Structure (28) depicts the relative, but not necessarily the absolute, configuration.

3 The Ester Alkaloids

General.—The electrophoretic mobilities of 27 pyrrolizidine alkaloids have been recorded in seven electrolytes.[17] The results show that electrophoresis at controlled pH often permits the separation of mixtures, depending on differences in molecular weight and base strength. A second electrophoretic method of separation depends on the ability of alkaloids containing vicinal glycol groups to form anionic complexes with sodium borate; this enables the separation of some alkaloids which are chromatographically indistinguishable.

The u.v. spectra of 23 pyrrolizidine alkaloids have been re-recorded, and correlated with the known structures of the alkaloids.[18] This has enabled some inconsistencies and errors in the earlier literature to be corrected.

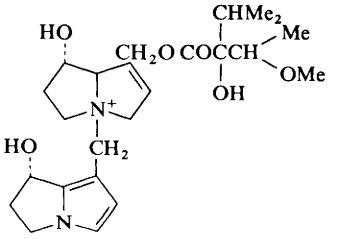
Monoester Alkaloids.—The dihydropyrrolizine analogues of the hepatotoxic pyrrolizidine alkaloids have been suggested[19] as possible toxic metabolites of the alkaloids. It is thus interesting to note that a minor constituent of the seeds of *Heliotropium europaeum* L., first isolated[20] in 1954, is one such dihydropyrrolizine derivative (29).[21] This quaternary base, which appears to be a genuine constituent of the plant and not simply an artifact, is presumably formed by alkylation of a molecule of heliotrine by dehydroheliotrine (30).[8] This reaction can also be achieved in dimethyl sulphoxide at 50 °C to give a product (isolated as the chloride) indistinguishable from authentic material.[21] Other examples of alkylation by the labile ester function in (30) and its analogues have also been recorded.[8,22]

The preparation of the dihydropyrrolizine analogues [*e.g.* (30)] of the unsaturated pyrrolizidine alkaloids has also been studied comprehensively.[8,22] Several procedures have been shown to be effective in one or more instances, *e.g.* oxidation by manganese dioxide in chloroform,[8,22] dehydrogenation by

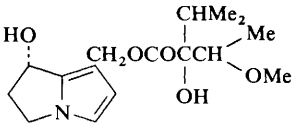
[16] G. Gafner and L. J. Admiraal, *Acta Cryst.*, 1969, **25B**, 2114.
[17] J. L. Frahn, *Austral. J. Chem.*, 1969, **22**, 1655.
[18] V. Šimánek, A. Klásek, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1969, **34**, 1832.
[19] A. R. Mattocks, *Nature*, 1968, **217**, 723.
[20] C. C. J. Culvenor, *Austral. J. Chem.*, 1954, **7**, 287.
[21] C. C. J. Culvenor and L. W. Smith, *Tetrahedron Letters*, 1969, 3603.
[22] A. R. Mattocks, *J. Chem. Soc.* (*C*), 1969, 1155.

2,3-dichloro-5,6-dicyanobenzoquinone, and reaction of the alkaloid *N*-oxide with acetic anhydride or ferrous sulphate.[22]

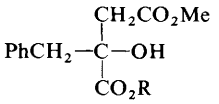
The pyrrolizidine alkaloid phalaenopsine T (31) has been isolated from *Phalaenopsis amabilis* Bl.;[23] its diastereoisomer phalaenopsine La (32) occurs in both *Ph. mannii* Rchb. f.[23] and *Kingiella taenialis* (*Lindl.*) Rolfe.[24] Both bases give (−)-dimethyl-2-benzylmalate on methanolysis. The basic product from phalaenopsine T proves to be trachelanthamidine, whereas phalaenopsine La gives the enantiomer laburnine.[23] Laburnine has also been encountered, in the form of its acetate, in *Vanda cristata* Lindl. (*fam.* Orchidaceae);[25] this is the first recorded investigation into the constituents of any *Vanda* species, and so far only laburnine acetate has been isolated. Another member of this family, *Chysis bractescens* Lindl., contains (+)-1-methoxycarbonylpyrrolizidine (33) of the same absolute configuration as lindelofidine, into which it is transformed by reduction with lithium aluminium hydride.[26]

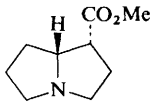


(29)

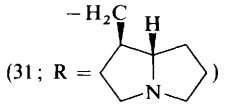


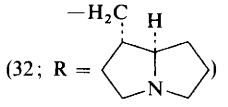
(30)





(33)





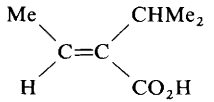
A group of Russian workers has achieved the first total syntheses in the pyrrolizidine ester-alkaloid series.[27] (±)-Trachelanthamidine, synthesised

[23] S. Brandänge and B. Lüning, *Acta Chem. Scand.*, 1969, **23**, 1151.
[24] S. Brandänge, I. Granelli, and B. Lüning, *Acta Chem. Scand.*, 1970, **24**, 354.
[25] B. Lindström and B. Lüning, *Acta Chem. Scand.*, 1969, **23**, 3352.
[26] B. Lüning and H. Tränkner, *Acta Chem. Scand.*, 1968, **22**, 2324.
[27] N. K. Kochetkov, A. M. Likhosherstov, and V. N. Kulakov, *Tetrahedron*, 1969, **25**, 2313.

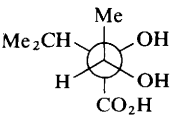
earlier,[28] was resolved by fractional crystallisation of its acid dibenzoyltartrate to yield, after hydrolysis, the two enantiomers, laburnine and (−)-trachelanthamidine (5). The diastereoisomeric mixture of synthetic 1-hydroxymethylpyrrolizidines also afforded (±)-isoretronecanol, which was similarly resolved into the enantiomers lindelofidine and isoretronecanol (23).

The acid components required for the synthesis of the ester alkaloids, (+)-trachelanthic and viridifloric acids, were synthesised by stereospecific routes, since the relative stereochemistry of the asymmetric centres in these acids was still uncertain. Eventually they were obtained by appropriate stereospecific (*cis* or *trans*) hydroxylation of *trans*-2-isopropylcrotonic acid (34), and its *cis*-isomer obtained by photochemical isomerisation. After resolution, (+)-trachelanthic acid was identified as the *threo*-2-isopropyl-2,3-dihydroxybutyric acid (35); the corresponding *erythro*-isomer was identified as viridifloric acid.

The ester alkaloids were then synthesised by base-catalysed transesterification of the methyl ester di-*O*-benzyl ether of the appropriate hydroxyacid with the appropriate 1-hydroxymethylpyrrolizidine, followed by debenzylation of the product by palladium-catalysed hydrogenolysis. In this way the synthesis of trachelanthamine (36),[27] its diastereoisomer viridiflorine (37),[27,29] and lindelofine (38) was achieved.[27,29]



(34)



(35)

The absolute configurations of the natural hydroxymethylpyrrolizidines have been established earlier, but only the relative configurations of the acid components of the alkaloids (36) and (37) were known. The absolute configurations of these acids have now been elucidated by correlation with 2-methyl-4-methoxypentan-3-one of proved absolute configuration. From these results the total absolute configurations shown on the following page have been deduced.[27,30]

Details of the work[31,32] on which the structures of the *Liparis* alkaloids are based have now been published.[33] Of these, kuramerine (39) from *L. krameri*

[28] A. M. Likhosherstov, L. M. Likhosherstov, and N. K. Kochetkov, *Zhur. obshchei Khim.*, 1963, **33**, 1801 (*Chem. Abs.*, 1963, **59**, 10143); A. M. Likhosherstov, V. N. Kulakov, and N. K. Kochetkov, *Zhur. obshchei Khim.*, 1964, **34**, 2798 (*Chem. Abs.*, 1964, **61**, 14734).

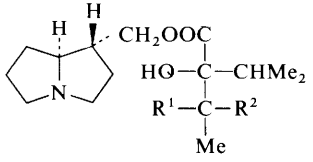
[29] A. M. Likhosherstov, V. N. Kulakov, and N. K. Kochetkov, *Zhur. obshchei Khim.*, 1967, **37**, 1012 (*Chem. Abs.*, 1968, **68**, 3045); V. N. Kulakov, A. M. Likhosherstov, and N. K. Kochetkov, *J. Gen. Chem.* (*U.S.S.R.*), 1968, **38**, 1674 [(from *Zhur. Obshchei Khim.*, 1968, **38**, 1718 (*Chem. Abs.*, 1969, **70**, 78207)].

[30] N. K. Kochetkov, A. M. Likhosherstov, and V. N. Kulakov, *Zhur. obshchei Khim.*, 1969, **39**, 1405 (*Chem. Abs.*, 1969, **71**, 70778).

[31] K. Nishikawa, M. Miyamura, and Y. Hirata, *Tetrahedron Letters*, 1967, 2597.

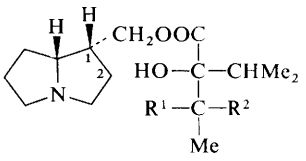
[32] K. Nishikawa and Y. Hirata, *Tetrahedron Letters*, 1967, 2591; 1968, 6289.

[33] K. Nishikawa, M. Miyamura, and Y. Hirata, *Tetrahedron*, 1969, **25**, 2723.



Trachelanthamine (36; $R^1 = H, R^2 = OH$)

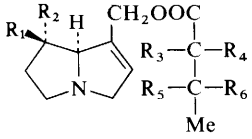
Viridiflorine (37; $R^1 = OH, R^2 = H$)



Lindelofine (38; $R^1 = H, R^2 = OH$)

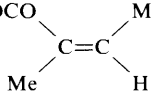
Cynaustraline (38; $R^1 = OH, R^2 = H$)

Cynaustine (38; $R^1 = OH, R^2 = H; \Delta^{1,2}$)

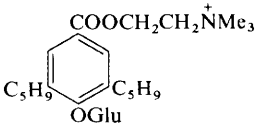


(38a)

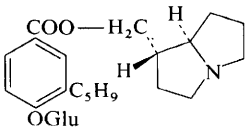
Supinine (38a; $R^1 = R^2 = R^5 = H, R^3 = R^6 = OH, R^4 = CHMe_2$)
Heleurine (38a; $R^1 = R^2 = R^5 = H, R^3 = OH, R^4 = CHMe_2, R^6 = OMe$)
Amabiline (38a; $R^1 = R^2 = R^6 = H, R^3 = R^5 = OH, R^4 = CHMe_2$)
Rinderine (38a; $R^1 = R^5 = H, R^2 = R^3 = R^6 = OH, R^4 = CHMe_2$)
Echinatine (38a; $R^1 = R^6 = H, R^2 = R^3 = R^5 = OH, R^4 = CHMe_2$)
Heliotrine (38a; $R^1 = R^5 = H, R^2 = R^3 = OH, R^4 = CHMe_2, R^6 = OMe$)
Indicine (38a; $R^1 = R^4 = R^5 = OH, R^2 = R^6 = H, R^3 = CHMe_2$)

Echiumine (38a; $R^1 =$  , $R^2 = R^5 = H, R^3 = R^6 = OH, R^4 = CHMe_2$

Franch. et Sav. is composed of choline, D-glucose, and nervogenic acid units, a structure which has now been established by synthesis of its tetra-acetyl derivative.[34] The structure of malaxine (40), from *Malaxis congesta* comb. nov. (Rchbf. f.)[35] and *L. bicallosa* Schltr., has also been confirmed by synthesis of its tetra-acetyl derivative.[34]



Kuramerine (39)

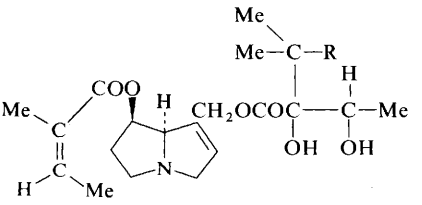


Malaxine (40)

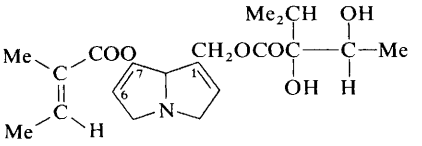
($C_5H_9 = -CH_2CH{=}CMe_2$)

[34] H. Tanino, S. Inoue, K. Nishikawa, and Y. Hirata, *Tetrahedron*, 1969, **25**, 3033.
[35] K. Leander and B. Lüning, *Tetrahedron Letters*, 1967, 3477.

Diester Alkaloids.—Three pyrrolizidine alkaloids have recently been isolated from two *Symphytum* species. The roots of *Symphytum officinale* L. (Comfrey) contain echimidine (41) and a new alkaloid, symphytine, which must possess the constitution (42) since hydrolysis affords retronecine, angelic acid, and (−)-viridifloric acid.[36] The position of the esterifying acids was determined by hydrogenation–hydrogenolysis, which afforded 7-(2′-methylbutyroyl)retronecanol. *Symphytum orientale* roots contain seven alkaloids, of which one newly discovered, anadoline (43), was further investigated.[37] Alkaline hydrolysis of anadoline gives rise to tiglic and trachelanthic acids, together with a doubly-unsaturated aminoalcohol. Accordingly, anadoline contains three double bonds but since it only contains three olefinic hydrogen atoms (n.m.r. spectrum), one double bond must be in the tiglic acid residue, a second is presumed to be at C-1 as it invariably is in the unsaturated pyrrolizidine alkaloids, and the third must be at position 6. The position of the esterifying acids was established by hydrogenation–hydrogenolysis, which, like symphytine and echimidine, gave 7-(2′-methylbutyroyl)retronecanol.[37]



Echimidine (41; R = OH)
Symphytine (42; R = H)



Anadoline (43)

The absolute configuration of monocrotalic acid (44), the necic acid component of monocrotaline (45), has been elucidated;[38] aside from the acid derived from retusamine, whose structure has been defined by *X*-ray crystallography,[39] this is the first necic acid component of a pyrrolizidine diester alkaloid containing an eleven-membered ring to have its stereochemistry unambiguously established.

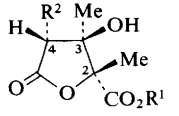
[36] T. Furuya and K. Araki, *Chem. and Pharm. Bull (Japan)*, 1968, **16**, 2512.
[37] A. Ulubelen and S. Doganca, *Tetrahedron Letters*, 1970, 2583.
[38] D. J. Robins and D. H. G. Crout, *J. Chem. Soc. (C)*, 1969, 1386.
[39] J. A. Wunderlich, *Chem. and Ind.*, 1962, 2089.

Monocrotaline (45) was reduced ($LiAlH_4$) to 2,3,4-trimethylpentane-1,2,3,5-tetraol (46). Periodate oxidation of (46), followed by hypobromite oxidation of the product, afforded 3-hydroxy-2-methylpropanoic acid, whose hydrazide (48) was shown to be enantiomeric with the known hydrazide[40] of *R*-configuration. The hydrazide from monocrotaline therefore has the *S*-configuration and monocrotalic acid has the *R*-configuration at C-4.

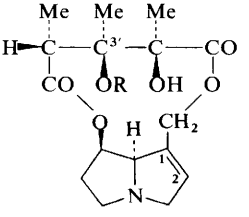
The configuration at C-3 in (44) was deduced by relating it to the configuration at C-4. The attempted dehydration of methyl monocrotalate (47) by phosphoryl chloride in pyridine, a reagent which normally exhibits a rigid requirement for a *trans*-orientation of the leaving groups, proceeded extremely slowly, a result which was interpreted as indicating a *cis*-disposition of hydrogen and hydroxy-group on positions 3 and 4. If this result is taken in conjunction with the proposal[41] of Cervinka *et al.*, that C-2 in monocrotalic acid has the *R*-configuration, the absolute configuration of monocrotalic acid (2*R*,3*R*,4*R*) must be as given in (44).[38]

Since the o.r.d. and c.d. curves of monocrotalic acid are very similar to the corresponding curves exhibited by trichodesmic acid (49), which is known independently[42] to have the same *relative* configuration at C-2, C-3, and C-4 as monocrotalic acid, the absolute configuration of trichodesmic acid must also be 2*R*,3*R*,4*R*.

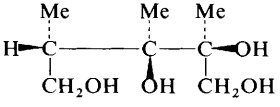
This conclusion concerning monocrotalic acid, which is at variance with the original proposal of Adams *et al.*,[43] is confirmed by a study of the n.m.r. spectra of the phenylboronate esters of monocrotaline and trichodesmine, which shows conclusively that these esters assume identical or nearly identical conformations. This is only possible if the configurations at C-2 and C-3 are the same in monocrotaline and trichodesmine. It is now believed that the original synthesis of



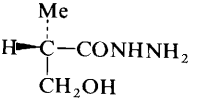
Monocrotalic acid (44; R^1 = H, R^2 = Me)
(47; R^1 = R^2 = Me)
Trichodesmic acid (49; R^1 = H, R^2 = $CHMe_2$)



Monocrotaline (45; R = H)
Spectabiline (54; R = $COCH_3$)
Grahamine (55; R = $COCHEtMe$)



(46)

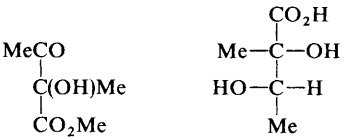


(48)

[40] J. Rétey and F. Lynen, *Biochem. Z.*, 1965, **342**, 256.
[41] O. Červinka, L. Hub, A. Klásek, and F. Šantavý, *Chem. Comm.*, 1968, 261.
[42] J. D. Edwards and T. Matsumoto, *J. Org. Chem.*, 1967, **32**, 2561.
[43] R. Adams, B. L. Van Duuren, and B. H. Braun, *J. Amer. Chem. Soc.*, 1952, **74**, 5608.

monocrotalic acid by Adams *et al.*[43] must have involved an anomalous *cis*-hydroxylation of a double bond by pertungstic acid, instead of the normal, expected *trans*-hydroxylation.[38]

The existence of this discrepancy between the conclusions of Adams *et al.*,[43] and of Robins and Crout[38] rendered desirable an independent proof of the absolute configuration at C-2 in monocrotalic acid. This has now been achieved by Robins and Crout[44] who degraded methyl monocrotalate to the ester (50) by means of dehydration, ozonolysis, and selective hydrolysis. Reduction of the ester with sodium borohydride followed by hydrolysis gave a mixture (not separated) of diastereoisomeric 2,3-dihydroxy-2-methylbutanoic acids, identical in R_F value with the authentic *threo*-isomer. The absolute configuration at C-2 in the acids derived from monocrotalic acid was then deduced by correlation with the (+)- and (−)-*threo*-2,3-dihydroxy-2-methylbutanoic acids of established absolute configuration.[45] *cis*-Hydroxylation of tiglic acid gave the racemic *threo*-acid which was resolved *via* its brucine salt to the 2*R*,3*S*-acid (51) and its enantiomer. Reduction of (−)-methyl acetolactate (50), derived from monocrotalic acid, with sodium borotritiide, followed by hydrolysis, gave a diastereoisomeric mixture of acids consisting either of the (2*R*,3*R*)- and (2*R*,3*S*)-acids or the (2*S*,3*R*)- and (2*S*,3*S*)-acids. Aliquot portions of the labelled acid mixture were then co-crystallised with the brucine salts of the authentic (2*R*,3*S*)- and (2*S*,3*R*)-acids, and the products recrystallised to constant activity. The activity of the (2*S*,3*R*)-salt rapidly fell to an insignificant value, but the activity of the (2*R*,3*S*)-salt fell to a constant value of 32% of the original value. Hence the mixture of labelled acids derived from monocrotalic acid consisted of 32% of the (2*R*,3*S*)-isomer and presumably 68% of the (2*R*,3*R*)-isomer. Hence C-2 in monocrotalic acid has the *R*-configuration, in confirmation of the earlier conclusions.[38,41]

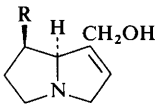


(50) (51)

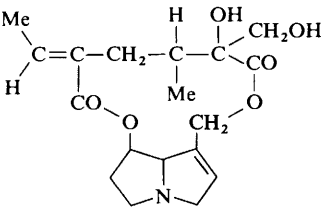
The oxidation of retronecine (52)[46] and supinidine (53)[47] by means of perbenzoic acid results in fairly rapid *N*-oxidation followed by a slow α-epoxidation requiring 6—18 days for completion at room temperature. In contrast, this reagent failed to oxidise monocrotaline (45), as also did peracetic acid and trifluoroperacetic acid.[48] The desired oxidation was eventually achieved with a

[44] D. J. Robins and D. H. G. Crout, *J. Chem. Soc.* (*C*), 1970, 1334.
[45] B. W. Christensen and A. Kjaer, *Proc. Chem. Soc.*, 1962, 307.
[46] L. J. Dry, M. J. Koekemoer, and F. L. Warren, *J. Chem. Soc.*, 1955, 59.
[47] C. C. J. Culvenor, G. M. O'Donovan, and L. W. Smith, *Austral. J. Chem.*, 1967, **20**, 757.
[48] C. C. J. Culvenor, G. M. O'Donovan, R. S. Sawhney, and L. W. Smith, *Austral. J. Chem.*, 1970, **23**, 347.

mixture of hydrogen peroxide, trifluoroacetic anhydride, and chloroform, the products being the α-epoxide (52%) and the β-epoxide (8%).



Retronecine (52; R = OH)
Supinidine (53; R = H)



Mucronatinine (56)

A new alkaloid, grahamine, has been isolated, together with monocrotaline (45), from the seeds of *Crotalaria grahamiana* R. Wight and Walk.-Arn., a perennial shrub indigenous to S. India.[49] The molecular formula, and the n.m.r. and mass spectra of grahamine suggested that it might be a macrocyclic diester alkaloid related to spectabiline (54); this was confirmed by the isolation of monocrotaline from the hydrolysis of grahamine by hydrochloric acid. From the n.m.r. spectrum it was argued that the acylating group present in grahamine (55) must be the 2-methylbutyroyl group, and this was also confirmed by the isolation of (−)-2-methylbutyric acid from the acidic product obtained on saponification. Grahamine is thus 3′-[(−)-2-methylbutyroyl]monocrotaline (55). The occurrence of 2-methylbutyric acid as an esterifying acid in a pyrrolizidine alkaloid is of some interest, since it has not been observed previously; however, its formation would need only a simple modification of the biosynthetic pathway that leads to the commonly encountered angelic acid.[49]

Mucronatinine (56), a new alkaloid which is the major constituent of the seeds of *Crotalaria mucronata* Desv., is a diastereoisomer of retrorsine; its structure was elucidated almost entirely by n.m.r. spectroscopy.[50]

Several Egyptian *Senecio* species have been investigated; of these, *S. aegyptius* L., *S. petasitis* DC., and the ubiquitous *S. vulgaris L.* were shown to contain senecionine, while *S. desfontainei* Druce (*S. coronopifolius* Desf.) yielded seneciphylline.[51] *S. aegyptius*, *S. petasitis*, and *S. mikanioides* (Walp.) Otto each contain unidentified alkaloids; the alkaloid from the last-named species appeared not to be identical with sarracine or its *N*-oxide, which have been isolated from this species on previous occasions.

Anacrotine and madurensine[52] have recently been isolated from *Crotalaria laburnifolia* Linn.[53] The structure (57), originally proposed[52] for madurensine,

[49] C. K. Atal, C. C. J. Culvenor, R. S. Sawhney, and L. W. Smith, *Austral. J. Chem.*, 1969, **22**, 1773.

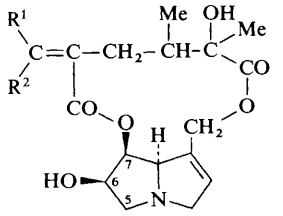
[50] N. S. Bhacca and R. K. Sharma, *Tetrahedron*, 1968, **24**, 6319.

[51] S. A. Gharbo and A. M. Habib, *Lloydia*, 1969, **32**, 503.

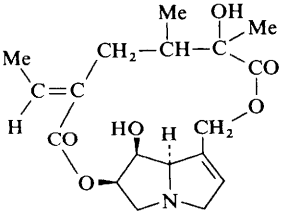
[52] C. K. Atal, K. K. Kapur, C. C. J. Culvenor, and L. W. Smith, *Tetrahedron Letters*, 1966, 537.

[53] T. R. Govindachari, S. J. Jadhav, B. S. Joshi, V. N. Kamat, P. A. Mohamed, P. C. Parthasarathy, S. J. Patankar, D. Prakash, D. F. Rane, and N. Viswanathan, *Indian J. Chem.*, 1969, **7**, 308.

a macrocyclic diester of the trihydroxypyrrolizidine, crotanecine, has now been shown[54] to be incorrect. The signal from the 5β-hydrogen in the n.m.r. spectrum of madurensine appears as a doublet ($J_{5\alpha,5\beta}$ − 15.0 Hz), whereas it is a triplet ($J_{5\alpha,5\beta}$ − 9.5 Hz, $J_{5\beta,6\alpha}$ 9.5 Hz) in the spectrum of its presumed geometrical isomer, anacrotine (58). Geometrical isomerism in the esterifying acid is not now considered a sufficient reason for the conformational difference which was postulated to account for the n.m.r. spectra, but closure of the diester ring at C-6 in madurensine would account for it satisfactorily. Consequently, madurensine is now regarded as the 1,6-diester (59), and the C*H*-OCOR signal (a triplet centred at δ 5.02) is due to a proton at C-6 having three neighbouring CH protons, but which is not visibly coupled with the β-proton at C-5. This assignment, and others in the spectrum of madurensine, have been confirmed by spin decoupling experiments. Similar spin decoupling experiments on anacrotine (58) confirm the placement of the ester linkage at C-7. Madurensine (59) is thus the first macrocyclic diester alkaloid in which the ester grouping is attached to C-6. Significantly, madurensine occurs in *Crotalaria agatiflora* Schweinf., together with its 7-acetyl derivative and 6-acetylanacrotine.[55]



(57; R^1 = Me, R^2 = H)
Anacrotine (58; R^1 = H, R^2 = Me)

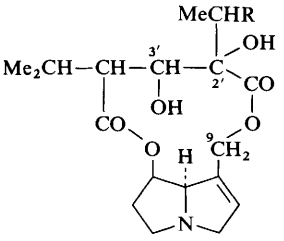


Madurensine (59)

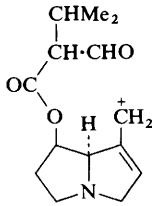
A full account of the work[56] leading to the elucidation of the structure of axillarine (60), the major alkaloid of *Crotalaria axillaris* Ait., has been published.[57] Axillaridine, $C_{18}H_{27}NO_6$, m.p. 148—152 °C, the more abundant of the two minor alkaloids, is the related deoxy compound (61). Its mass spectrum exhibits the characteristic peaks of a retronecine diester, and also a peak at *m/e* 250 which is attributed to the ion (62), generated by a McLafferty rearrangement of the radical-ion produced by fragmentation of (61) at the C(9)–oxygen bond. This rearrangement necessarily involves the hydroxy-group at position 3′, and since axillaridine contains a 1,2-diol function it must also carry a hydroxy-group at position 2′; the remaining substituent at position 2′ must then be an ethyl group. The n.m.r. spectra of axillaridine and its derivatives, including axillarine, are fully in accord with this conclusion.

[54] C. C. J. Culvenor, L. W. Smith, and R. I. Willing, *Chem. Comm.*, 1970, 65.
[55] C. C. J. Culvenor and L. W. Smith, unpublished work, reported in ref. 54.
[56] D. H. G. Crout, *Chem. Comm.*, 1968, 429.
[57] D. H. G. Crout, *J. Chem. Soc.* (*C*), 1969, 1379.

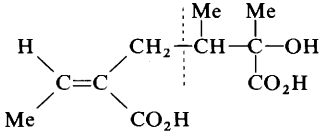
Axillarine and axillaridine therefore contain C_{10} necic acid components belonging to a new structural type. The four groups of necic acids previously known, of which senecic acid (63) may be cited, contain a common C_5 structural component [indicated to the right of the dotted line in (63)], which suggests that in the biosynthesis of the necic acids this unit is coupled to various intermediates derived from common amino-acids. In the biosynthesis of axillarine and axillaridine, however, it would appear that this same C_5 unit is involved, but with a different mode of coupling to the other 5-carbon unit. This adds credence to the earlier proposal that in the biosynthesis of the necic acids, the common C_5 unit (derived from isoleucine?) is coupled as an intact unit.[57]



(60; R = OH)
(61; R = H)



(62)



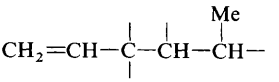
(63)

Clivorine, the alkaloid of *Ligularia clivorum* Maxim., was earlier shown to be a pyrrolizidine alkaloid whose basic constituent is otonecine (64).[58] The acid component is a hydroxydicarboxylic acid which readily lactonises, on attempted isolation, to clivonecic acid (65). The structure of this acid has now been firmly established[59] on the basis of chemical and spectroscopic evidence, and its stereochemistry has also been discussed. The present proposal[41] is that clivonecic acid has the *S*-configuration at C-2 since the o.r.d. spectrum of tetrahydroclivonecic acid exhibits a positive Cotton effect, in agreement with the modified octant rule.[60]

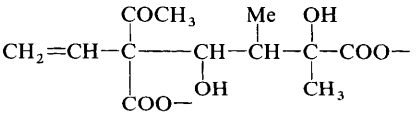
The structure of the dicarboxylic acid unit in the parent alkaloid clivorine, $C_{21}H_{29}NO_8$, is not immediately apparent, since hydrolysis to otonecine and clivonecic acid is accompanied by loss of two carbon atoms, which were shown to be eliminated as acetic acid.[61] This facile loss of acetic acid suggests that the

[58] A. Klásek, P. Vrublovský, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1967, **32**, 2512.
[59] A. Klásek, N. Neuner-Jehle, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1969, **34**, 1459.
[60] G. Snatzke, H. Ripperger, C. Horstmann, and K. Schreiber, *Tetrahedron*, 1966, **22**, 3103.
[61] A. Klásek, P. Sedmera, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1970, **35**, 956.

alkaloid is a substituted acetoacetic ester which, since it gives a negative response to iron(III) chloride, is presumably αα-disubstituted. The presence of an acetyl group in the alkaloid is consistent with the signal at 2.065 p.p.m. (3H, s) in the 100 MHz n.m.r. spectrum. Three other methyl signals are also present, namely, singlets at 2.04 p.p.m. (NMe) and 1.51 p.p.m. (Me—C(—)—O), and a doublet at 1.165 p.p.m. (MeCH—). There is no signal due to a methyl group attached to a double bond, as might be expected from the structure of clivonecic acid. Instead, the n.m.r. spectrum of the alkaloid discloses the presence of a vinyl group, which was chemically established by isolation of formaldehyde from the ozonolysis of clivorine. On the basis of these results and double resonance experiments the fragment:

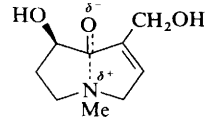


was shown to be present in clivorine. Having regard to the structure of clivonecic acid and the proved presence (i.r., n.m.r.) of two hydroxy-groups in clivorine this may be expanded to:

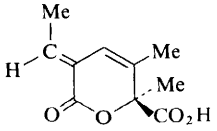


and the complete structure of clivorine is (66).[61] The formation of clivonecic acid is thus seen to involve acid fission of the acetyl group in the substituted acetoacetic ester, with concomitant dehydration, isomerisation, and lactonisation.

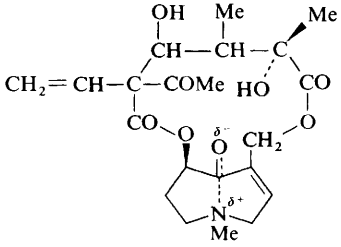
The absolute configuration at C-2 of some other necic acids has also been established by examination of their o.r.d. spectra.[41] In contrast to clivonecic



Otonecine (64)



Clivonecic acid (65)



Clivorine (66)

acid, dihydrosenecic acid lactone and tetrahydroseneciphyllic acid lactone (both stereoisomers of tetrahydroclivonecic acid) possess the *R*-configuration at C-2.

4 Pharmacological Aspects

An excellent volume on the pyrrolizidine alkaloids has recently been published.[62] The chemistry of these alkaloids is briefly discussed, but considerable emphasis is placed on their pharmacology and pathogenicity. In another reference, Culvenor and his collaborators[63] discuss the hepatotoxicity, antimitotic properties, and the metabolism of these alkaloids. The significance of the alkylating properties in relation to the antimitotic activity, and the role of pyrroles formed *in vivo*, are also discussed.

A series of diesters of retronecine (64), and some acyl derivatives of indicine, monocrotaline (55), and retrorsine have been prepared for toxicological comparison with the natural ester alkaloids.[64]

[62] L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids,' North Holland Publishing Co., Amsterdam, 1968.
[63] C. C. J. Culvenor, D. T. Downing, and J. A. Edgar, *Ann. N.Y. Acad. Sci.*, 1969, **163**, 837.
[64] A. R. Mattocks, *J. Chem. Soc.* (*C*), 1969, 2698.

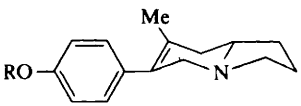
6
The Indolizidine Group

BY J. E. SAXTON

1 *Ipomoea* Alkaloids

The seeds of the moonflower, *Ipomoea alba* L. (fam. Convolvulaceae), have earlier been shown to contain ergoline alkaloids,[1] but in a more recent investigation[2] they have also been shown to contain hydroindolizine alkaloids. Three alkaloids have been isolated, namely, ipalbine, ipalbidine, and a third, unidentified base. Ipalbine (1) is a D-glucoside which is readily hydrolysed by acid to ipalbidine (2), $C_{15}H_{19}NO$, m.p. 147–148 °C. Ipalbidine is a phenolic tertiary base which contains a *C*-methyl group and a double bond. Selenium dehydrogenation gives a crystalline solid, identified as 5-*p*-hydroxyphenyl-4-methyl-2-propylpyridine. The position of the methyl signal, the AA'BB' pattern of signals owing to the aromatic protons, and the absence of olefinic protons in the n.m.r. spectrum of ipalbidine are all consistent with the structure (2). Further support comes from the mass spectrum of ipalbidine and the n.m.r. spectrum of dihydroipalbidine.

In the n.m.r. spectrum of the parent glucoside ipalbine, an ill-defined doublet at τ 5.14 is assigned to the anomeric proton in a β-D-glucoside, since it resembles in appearance and chemical shift the analogous proton in phenyl β-D-glucopyranoside.[2]



Ipalbine (1, R = β-D-glucosyl)
Ipalbidine (2, R = H)

2 *Elaeocarpus* Alkaloids

A new family of indolizidine alkaloids has been isolated from three species of the *Elaeocarpus* genus (fam. Elaeocarpaceae). *E. polydactylus* Schltr., a large, spreading tree, indigenous to New Guinea, contains three interrelated alkaloids of

[1] A. Der Marderosian, *Lloydia*, 1967, **30**, 23; *Amer. J. Pharm.*, 1967, **139**, 19.
[2] J. M. Gourley, R. A. Heacock, A. G. McInnes, B. Nikolin, and D. G. Smith, *Chem. Comm.*, 1969, 709.

which (±)-elaeocarpine, $C_{16}H_{19}NO_2$, was shown to have the structure (3) by *X*-ray crystal structure analysis of its hydrobromide.[3,4,7] The second major alkaloid, (±)-isoelaeocarpine (4), is clearly a stereoisomer of (±)-elaeocarpine since interconversion of the two alkaloids is easily accomplished by methanolic potassium hydroxide. The u.v. and mass spectra of elaeocarpine and isoelaeocarpine also indicate that these alkaloids are stereoisomers, while the presence of strong Bohlmann bands in the i.r. spectra suggests that the indolizidine ring junction in both alkaloids is *trans*. The n.m.r. spectra of these alkaloids are complex, but the multiplet owing to the C-7 proton in elaeocarpine is consistent with its diaxial relationship with the proton at C-8 (as shown by the *X*-ray analysis), since $J_{7,8} = 11.8$ Hz, and $\frac{1}{2}(J_{7,6\beta} + J_{7,6\alpha}) = 7.8$ Hz. In contrast, the analogous coupling constants in the n.m.r. spectrum of isoelaeocarpine are very small [$J_{7,8} = 2.1$ Hz, $\frac{1}{2}(J_{7,6\beta} + J_{7,6\alpha}) = 2.8$ Hz], an observation which can only be interpreted on the basis of an equatorial disposition of the C-7 proton with regard to ring C. In confirmation the C-8 proton can be shown to be axial, since $J_{8,9} = 10$ Hz.

The interconversion of elaeocarpine and isoelaeocarpine presumably involves cleavage of ring B (*cf.* arrows in 3) to give an intermediate anion (5) which can recyclise to give an equilibrium mixture of the two alkaloids.[4]

(+)-Isoelaeocarpicine, a minor constituent of *E. polydactylus*, is considered to have the structure (6),[4] and is so named because it corresponds in stereochemistry with isoelaeocarpine. The molecular formula of isoelaeocarpicine is established by its mass spectrum, and its relationship with the two major alkaloids is demonstrated by the formation of a mixture of elaeocarpine and isoelaeocarpine when isoelaeocarpicine is heated in methanolic alkali.* In consonance with the constitution (6), isoelaeocarpicine is phenolic and is readily methylated by diazomethane. Mild acetylation affords a phenolic acetate, but prolonged reaction gives an *N*-acetyl compound, formulated as (7), whose formation presumably proceeds *via* the intermediate (8).

The relative stereochemistry implied in structure (6) was deduced from an analysis of the n.m.r. multiplets owing to the C-7 and C-8 protons in a manner exactly analogous to that applied to the study of isoelaeocarpine.[4]

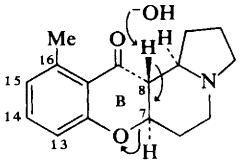
Elaeocarpus dolichostylis Schltr., the second *Elaeocarpus* species to be investigated, is also a large tree indigenous to the rain forests of New Guinea.[5]

[3] S. R. Johns, J. A. Lamberton, A. A. Sioumis, and J. A. Wunderlich, *Chem. Comm.*, 1968, 290.

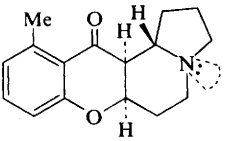
[4] S. R. Johns, J. A. Lamberton, A. A. Sioumis, and R. I. Willing, *Austral. J. Chem.*, 1969, **22**, 775.

[5] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Chem. Comm.*, 1968, 1324; *Austral. J. Chem.*, 1969, **22**, 793.

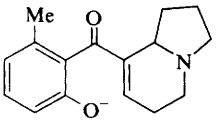
*The rotation values and the *X*-ray analysis show that natural elaeocarpine and isoelaeocarpine are racemic. (+)-Isoelaeocarpicine is significantly dextrorotatory ($[\alpha]_D$ +29°), but its optical purity remains to be determined. The reaction of (+)-isoelaeocarpicine with alkali affords elaeocarpine having a low positive rotation ($[\alpha]_D$ +20°) and virtually racemic isoelaeocarpine, but since optically active elaeocarpine and isoelaeocarpine are known to racemise under these conditions, the experiment gives no information concerning the optical purity of (+)-isoelaeocarpicine.[4]



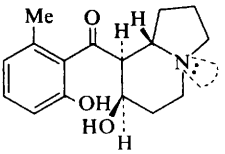
(+)-Elaeocarpine (3)



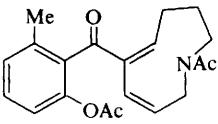
(−)-Isoelaeocarpine (4)



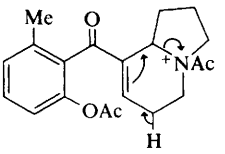
(5)



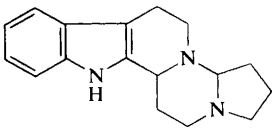
Isoelaeocarpicine (6)



(7)



(8)



Elaeocarpidine (9)

The leaves of this tree contain elaeocarpidine (9) as major constituent,[6] together with (+)-elaeocarpiline (10) and (−)-isoelaeocarpiline (11); trace amounts of elaeocarpine and isoelaeocarpine were also detected.[5]

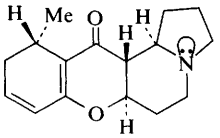
(+)-Elaeocarpiline, $C_{16}H_{21}NO_2$, is a conjugated dienone (u.v. and i.r. spectra) which may be hydrogenated to an $\alpha\beta$-unsaturated ketone [(+)-13,14,15,16-tetrahydro-elaeocarpine, 12], and dehydrogenated to (+)-elaeocarpine, $[\alpha]_D$ + 206°. The two hydrogen atoms removed in the dehydrogenation of (+)-elaeocarpiline (10) must be at C-15 and C-16, since the n.m.r. spectrum of (+)-elaeocarpiline exhibits a three-proton doublet at τ 9.05 owing to the methyl group. The spectrum also contains signals owing to two olefinic protons, of which that at C-14 appears as a complex multiplet centred on τ 3.73, and that at C-13 appears as a double doublet at τ 4.15 ($J_{13,14}$ = 10 Hz, $J_{13,15}$ = 2.9 Hz) resulting

[6] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Chem. Comm.*, 1968, 410; *Austral. J. Chem.*, 1969, **22**, 801.

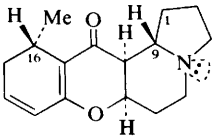
[7] J. A. Wunderlich, *Acta Cryst.*, 1969, **25B**, 1436.

from vicinal coupling and allylic coupling with one of the protons of the C-15 methylene group. The C-7 proton signal closely resembles that of the analogous proton in elaeocarpine, but a complete analysis was not carried out since chemical confirmation of its stereochemistry was available.

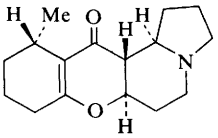
By similar methods the structure and relative stereochemistry of (−)-isoelaeocarpiline (11) were established;[5] only the configuration at C-16 remained unknown. This was deduced from a study of the reduction of (−)-isoelaeocarpiline by sodium borohydride. The product, (−)-tetrahydroisoelaeocarpine (12), is identical with the hydrogenation product, the carbonyl group remaining unaffected. Clearly, as with isoelaeocarpine,[4] which is reduced by borohydride to give only one (13) of the two possible C-10 epimeric alcohols, the carbonyl group in (−)-isoelaeocarpiline is resistant to attack on one side (the β-face on the basis of 11) by borohydride, owing to steric hindrance by β-hydrogen atoms attached to C-1 and C-9. Attack at the α-face in (11) can also be severely hindered by an appropriately oriented, *i.e.* α-oriented, methyl group at position 16. Hence (−)-isoelaeocarpiline has the complete relative stereochemistry shown in (11).[5]



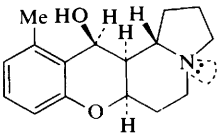
(+)-Elaeocarpiline (10)



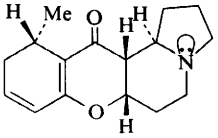
(−)-Isoelaeocarpiline (11)



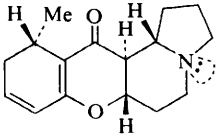
(12)



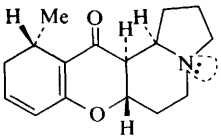
(13)



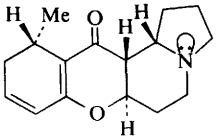
(+)-Epi-isoelaeocarpiline (14)



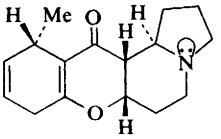
(−)-Epielaeocarpiline (15)



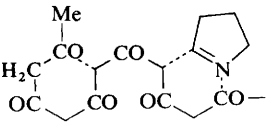
(+)-Epialloelaeocarpiline (16)



(−)-Alloelaeocarpiline (17)



(+)-Pseudoepi-isoelaeocarpiline (18)



(19)

In a later study[8] the structures and absolute configurations of seven isomeric alkaloids, isolated from *E. sphaericus* (Gaertn.) K. Schum., were established. Of these, the major alkaloid is (−)-isoelaeocarpiline, which was shown to have the absolute configuration expressed in (11) by oxidation to (*S*)(−)-methylsuccinic acid. (−)-Isoelaeocarpiline thus has the absolute configuration 7*R*,8*S*, 9*S*,16*S*, and since dehydrogenation gives (−)-isoelaeocarpine (4), the latter has the absolute configuration 7*R*,8*S*,9*S*.

The third alkaloid, (+)-epi-isoelaeocarpiline, m.p. 98—100 °C, has spectroscopic properties very similar to those of (11), and affords on dehydrogenation a mixture of (+)-isoelaeocarpine (enantiomer of 4), and (+)-dihydroepi-isoelaeocarpiline. Since the n.m.r. spectrum indicates that the configuration at C-16 relative to that at C-7, C-8, and C-9 is opposite to that in (11), (+)-epi-isoelaeocarpiline (14) must have the absolute configuration 7*S*,8*R*,9*R*,16*S*.

The close similarity between the o.r.d. spectra of (+)-elaeocarpiline (10) and (+)-epi-isoelaeocarpiline (14) indicates that C-16 and C-8, which are associated with the absorbing chromophores, have the same absolute configuration. Since the relative stereochemistry of (+)-elaeocarpiline, with the exception of the configuration at C-16, had been deduced earlier (see above), the complete absolute configuration of (+)-elaeocarpiline (10) is 7*R*,8*R*,9*R*,16*S*. Dehydrogenation of (10) affords (+)-elaeocarpine (3), which is therefore 7*R*,8*R*,9*R*.

By reasoning exactly analogous to that employed in the case of (+)-epi-isoelaeocarpiline, the fourth alkaloid, (−)-epielaeocarpiline, which affords (−)-elaeocarpine on dehydrogenation, may be shown to have the absolute configuration shown in (15).

The fifth alkaloid, (+)-epialloelaeocarpiline (16), m.p. 136—137 °C, is also a conjugated dienone (u.v. spectrum), and is yet another stereoisomer of elaeocarpiline (n.m.r. spectrum). Dehydrogenation gives a complex mixture of four products from which 7*S*,8*R*,9*R*-(+)-isoelaeocarpine (enantiomer of 4) may be isolated, and when (+)-epialloelaeocarpiline is chromatographed on silica-gel t.l.c. plates, isomerisation occurs in part to give some (+)-epi-isoelaeocarpiline (14). The alkaloid itself, however, appears to possess *trans*-diaxial hydrogen atoms at positions 7 and 8 (n.m.r. evidence). This curious result is explained on the basis of the structure (16) for (+)-epialloelaeocarpiline by assuming that the preferred conformation contains a *cis*-C–D ring fusion. Its conversion into (+)-epi-isoelaeocarpiline (14) can then proceed by epimerisation at C-8 with a subsequent

[8] S. R. Johns, J. A. Lamberton, A. A. Sioumis, H. Suares, and R. I. Willing, *Chem. Comm.*, 1970, 804.

chair-to-chair inversion of ring C that changes the C–D ring junction from *cis* to *trans* and requires also inversion of the nitrogen configuration.[8]

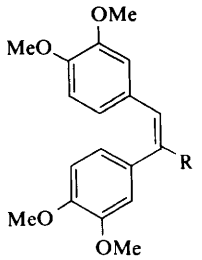
A similar situation is encountered with the sixth alkaloid, (−)-alloelaeocarpiline (17), which isomerises in part during chromatography on silica gel to (−)-isoelaeocarpiline (11). In consequence, (−)-alloelaeocarpiline (17) is regarded as the C-8 epimer of (11) with a *cis*-C–D ring junction.

The seventh alkaloid, (+)-pseudoepi-isoelaeocarpiline (18), is a structural isomer of elaeocarpiline. It is an $\alpha\beta$-unsaturated ketone, which on hydrogenation affords (+)-dihydroepi-isoelaeocarpiline (dihydro-14). The n.m.r. spectrum of (18) contains a 3-proton doublet at τ 8.87 owing to the C-16 methyl group, and also contains signals consistent with the presence of a C-14—C-15 double bond. Hence (+)-pseudoepi-isoelaeocarpiline (18) has the absolute configuration 7*S*,8*R*,9*R*,16*S*.

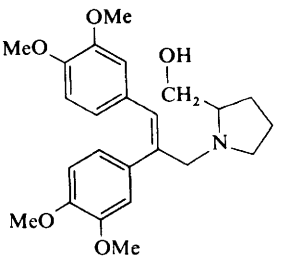
The biosynthetic origin of these alkaloids is of some interest. One non-alkaloidal constituent of *E. polydactylus* is 2-hydroxy-6-methylacetophenone,[4] a structural unit which may be clearly discerned in the alkaloids. This unit is very probably derived from acetate, hence the alkaloids may be formed by the condensation of a polyketomethylene chain with ornithine, as depicted in (19). If so, it would appear that elaeocarpiline and its stereoisomers precede the other alkaloids in the biosynthetic sequence; aromatisation and racemisation then constitute the final steps.[5]

3 The Tylophorine Group

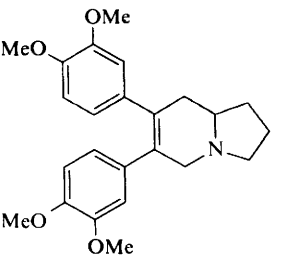
The structure proposed for septicine (20), the dehydroindolizidine constituent of *Ficus septica*, has recently been confirmed by two independent syntheses.[9,10] The first synthesis proceeded from veratraldehyde, which was condensed with homoveratric acid to give the unsaturated acid (21); this was then converted into the primary chloride (22) by standard methods. Alkylation of L-prolinol with this chloride gave the amino-alcohol (23), which was converted into its *O*-methanesulphonate ester. Reaction of this ester with sodium hydride in anhydrous



(21, R = CO_2H)
(22, R = CH_2Cl)



(23)

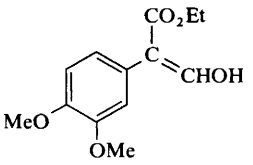


Septicine (20)

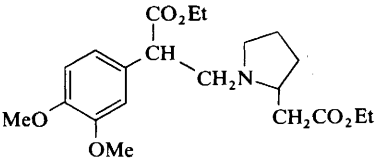
[9] J. H. Russel and H. Hunziker, *Tetrahedron Letters*, 1969, 4035.
[10] T. R. Govindachari and N. Viswanathan, *Tetrahedron*, 1970, **26**, 715.

dimethylformamide then afforded septicine (20). This method of ring closure was adopted since attempts to cyclise (23) or its methanesulphonate under Friedel–Crafts conditions gave only small yields of the desired product.[9]

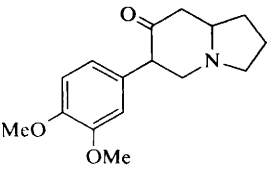
The second synthesis[10] of septicine used as starting material ethyl homoveratrate, which was formylated to the α-hydroxymethylene derivative (24). Controlled reduction of (24) with sodium borohydride gave mainly the desired β-hydroxyester, which was converted into the chloride and condensed with ethyl 2-pyrrolidinyl acetate to yield the diester (25). Dieckmann cyclisation of (25) followed by hydrolysis and decarboxylation then yielded the ketone (26), which reacted with 3,4-dimethoxyphenyl-lithium to give the tertiary alcohol (27). Finally, dehydration of (27) by means of sulphuric acid gave (±)-septicine (20).[10]



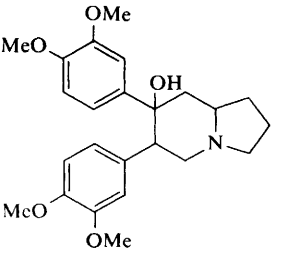
(24)



(25)



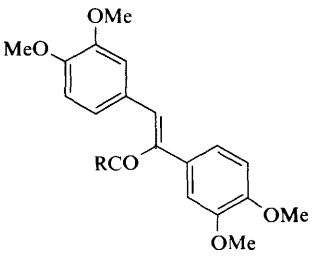
(26)



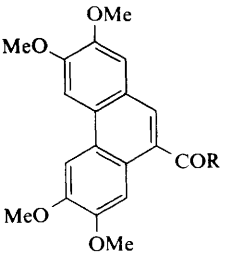
(27)

A new synthesis[11] of tylophorine (34) utilises the photolytic cyclisation of 3,4-dimethoxy-α-(3,4-dimethoxyphenyl)cinnamic acid methyl ester (28), which affords methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate (29). Condensation of the acid from (29) with methyl prolinate in the presence of dicyclohexylcarbodi-imide gave the amide (30), which could also be obtained by photolysis of the amide (31). *O*-Alkylation of the amide function in (30) by means of triethyloxonium fluoroborate followed by reduction with sodium borohydride then gave the amino-ester (32), the ester group remaining unaffected by this sequence of reactions. Cyclisation of the corresponding acid (33) with polyphosphoric acid gave the desired pentacyclic ketone, which was finally reduced by the Clemmensen method to yield (±)-tylophorine (34).[11]

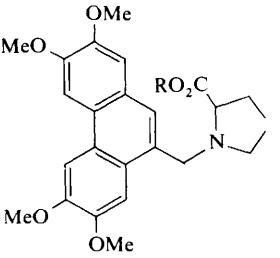
[11] R. B. Herbert and C. J. Moody, *Chem. Comm.*, 1970, 121.



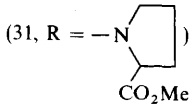
(28, R = OMe)



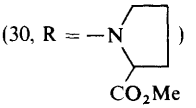
(29, R = OMe)



(32, R = Me)

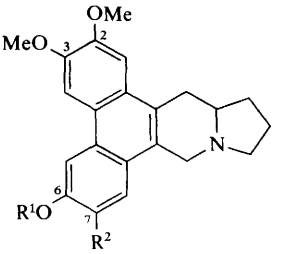


(31, R = —N)

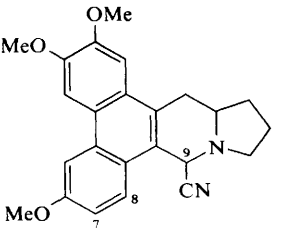


(30, R = —N)

(33, R = H)



Tylophorine (34, R^1 = Me, R^2 = OMe)
Alkaloid A (35, R^1 = Me, R^2 = H)
Alkaloid C (36, R^1 = R^2 = H)



(37)

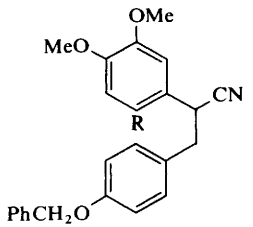
The aerial parts of *Cynanchum vincetoxicum* (L.) Pers. (Asclepiadaceae) contain three phenanthroindolizidine alkaloids, which have been shown to be tylophorine (34), 7-demethoxytylophorine (Alkaloid A, 35), and 7-demethoxy-demethyltylophorine (Alkaloid C, 36).[12] The trimethoxy-base (35) has also been isolated, together with two unidentified alkaloids, from the dried roots of the same plant,[13] and from *Vincetoxicum officinale* Moench., in which it occurs along with tylophorine.[14] The early work[14] on this trimethoxy-base indicated that it was either (35) or the 3,6,7-trimethoxy isomer, but this latter possibility has now been excluded.[12] The n.m.r. spectrum did not allow a distinction to be made between (35) and the 3,6,7-trimethoxy analogue, hence the alkaloid was oxidised by mercuric acetate, and the immonium salt so obtained was

[12] W. Wiegrebe, L. Faber, H. Brockmann, H. Budzikiewicz, and U. Krüger, *Annalen*, 1969, **721**, 154.
[13] A. Háznagy, L. Tóth, and K. Szendrei, *Pharmazie*, 1965, **20**, 649.
[14] M. Pailer and W. Streicher, *Monatsh.*, 1965, **96**, 1094.

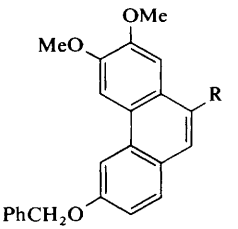
converted into the nitrile (37) by reaction with potassium cyanide. In the n.m.r. spectrum of (37) the signals owing to the hydrogens at C-1, C-4, and C-5 were unchanged in chemical shift, but that owing to the proton at C-8 was shifted downfield as the result of deshielding by the nitrile function, and was clearly observed as a doublet at τ 2.02. The C-7 proton signal was shifted very slightly downfield, and appeared as a double doublet, in consonance with the structure (35).[12]

The third, phenolic alkaloid (Alkaloid C) is evidently a demethyl derivative of Alkaloid A (35), since the latter is the product of methylation of Alkaloid C.[12]

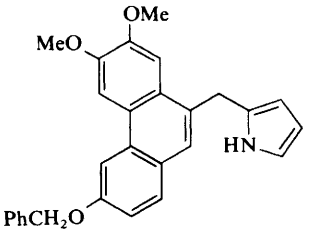
These structures for Alkaloids A and C have since been confirmed by total synthesis.[15] Condensation of 2-nitro-4,5-dimethoxybenzyl cyanide with 4-benzyloxybenzyl chloride gave the nitrile (38) which was converted into the phenanthrene derivative (40) by the Pschorr synthesis *via* the amine (39), followed by dehydrogenation. The phenanthrene nitrile (40) was converted by standard methods into the related chloromethylphenanthrene derivative (41), which condensed with pyrrolemagnesium bromide to give a mixture of two pyrroles, in which the desired isomer (42) predominated. Hydrogenolysis and hydrogenation then afforded the phenolic pyrrolidine (43), which was formylated and cyclised by means of phosphorus oxychloride. Finally, reduction with sodium borohydride gave (±)-Alkaloid C (36), identical in spectroscopic properties with



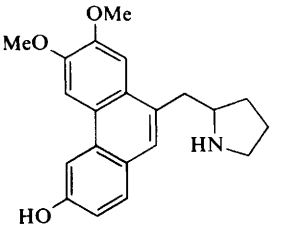
(38, R = NO_2)
(39, R = NH_2)



(40, R = CN)
(41, R = CH_2Cl)



(42)



(43)

[15] W. Wiegrebe, L. Faber, and H. Budzikiewicz, *Annalen*, 1970, **733**, 125.

natural (−)-Alkaloid C. Methylation gave (±)-Alkaloid A, which was identical in all properties with racemic Alkaloid A (35), prepared by mercuric acetate oxidation of (−)-Alkaloid A, followed by reduction of the tetradehydro-derivative so obtained.[15]

7
Quinolizidine Alkaloids

BY J. E. SAXTON

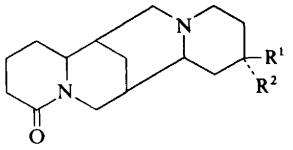
1 Lupine Group

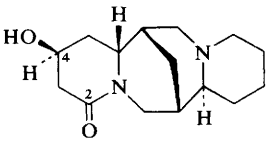
A. Occurrence, and Isolation of New Alkaloids.—In earlier investigations the branches of *Genista cinerea* D.C. (Leguminosae) were shown to contain cineverine (1)[1] and cinegalline (2),[2] two esters of (+)-13-hydroxylupanine. The same workers have now isolated a third ester alkaloid, cinegalleine (3), which proves to be the 5-hydroxy-3,4-dimethoxybenzoate of (+)-13-hydroxylupanine.[3] *Genista equisetiformis* Spach., which is indigenous to Southern Spain, also contains quinolizidine alkaloids, of which four have been identified.[4] The major alkaloids are *N*-methylcytisine and cytisine; minor constituents are anagyrine and sparteine. Several other alkaloids, present in trace amounts, were not identified. Retamine, which is claimed to be a characteristic constituent of this genus, is not apparently present. *Genista angulata* contains four alkaloids,[5] of which three were definitely identified as cytisine, anagyrine, and lupanine. A point of chemotaxonomic interest arises in connection with the alkaloid content of *Genista hystrix* Lange. This species apparently does not contain quinolizidine alkaloids, but contains ammodendrine and hystrine.[6]

The leaves and stems of *Thermopsis montana* Nutt. (*T. fabacea* Hook.) contain five alkaloids, four of which are also contained in the flowers and fruits.[7] Three other alkaloids are also present in trace amounts in all parts of the plant. The five alkaloids isolated and characterised are cytisine and *N*-methylcytisine (previously isolated[8]), hydroxylupanine, anagyrine, and thermopsine; apparently *N*-methylcytisine is not present in the flowers and fruits. Two of the minor alkaloids were tentatively identified as lupanine and 17-oxosparteine.

In addition to several other alkaloids *Lupinus nuttallii* S. Wats. contains a hitherto unknown base, nuttalline, $C_{15}H_{24}N_2O_2$, m.p. 108–109 °C, $[\alpha]_D^{26°}$ +

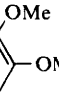
[1] G. Faugeras and R. R. Paris, *Compt. rend.*, 1966, **263***D*, 436.
[2] G. Faugeras and R. R. Paris, *Compt. rend.*, 1968, **267***D*, 538.
[3] G. Faugeras and R. R. Paris, *Compt. rend.*, 1970, **270***D*, 203.
[4] G. Faugeras and M. Paris, *Ann. pharm. franc.*, 1969, **27**, 269.
[5] G. Faugeras and M. Paris, *Plant. Med. Phytother.*, 1969, **3**, 175 (*Chem. Abs.*, 1970, **72**, 75688).
[6] E. Steinegger and F. Schnyder, *Pharm. Acta Helv.*, 1970, **45**, 157.
[7] W. J. Keller and F. R. Cole, *Lloydia*, 1969, **32**, 498.
[8] A. A. Ryabinin and E. M. Il'ina, *Zhur. priklad. Khim.*, 1955, **28**, 663 (*Chem. Abs.*, 1955, **49**, 13597).



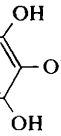


Nuttalline (4)

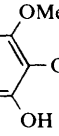
Cineverine (1, R = OCO–C$_6$H$_3$(OMe)–OMe)



Cinegalline (2, R = OCO–C$_6$H$_3$(OH)–OMe)



Cinegalleine (3, R = OCO–C$_6$H$_3$(OMe)–OMe)



13-Hydroxylupanine (14a, R^1 = H, R^2 = OH)
13-Epihydroxylupanine (14b, R^1 = OH, R^2 = H)

25.3° (EtOH).[9] Nuttalline is a hydroxylactam of the sparteine series, and exhibits i.r. absorption bands characteristic of a *trans*-quinolizidine derivative; its properties indicate that it is (+)-4α-hydroxy-2-oxosparteine (4), and it is the first example of a naturally-occurring 2,4-dioxygenated sparteine. Nuttalline gives a complicated mixture of products when reduced by lithium aluminium hydride, but with sodium borohydride affords deoxonuttalline [(−)-4α-hydroxysparteine], which can be converted by dehydration and hydrogenation into (−)-sparteine.

Similar dehydration and hydrogenation of nuttalline itself gives the known (+)-lupanine [(+)-2-oxosparteine]. The position of the hydroxy-group is established by Oppenauer oxidation of nuttalline, which yields a ketolactam possessing the spectrographic properties of a 1,3-dicarbonyl compound. Finally, the configuration of the hydroxy-group is rigorously established by reduction of the ketolactam with lithium aluminium hydride, which gives the 4-hydroxy epimer of deoxonuttalline, identified as the known 4β-hydroxysparteine.[9]

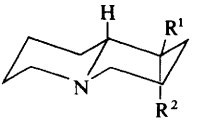
Previous extractions[10,11] of *Sophora griffithii* Stocks resulted in the isolation of pachycarpine [(+)-sparteine] and cytisine. In addition to these bases, the

[9] S. I. Goldberg and V. M. Balthis, *Chem. Comm.*, 1969, 660.
[10] S. Y. Yunusov and N. V. Plekhanova, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1957, No. 8, 17 (*Chem. Abs.*, 1958, **52**, 13017).
[11] A. P. Yakovleva and P. S. Massagetov, *Zhur. obshchei Khim.*, 1960, **30**, 348 (*Chem. Abs.*, 1960, **54**, 22698).

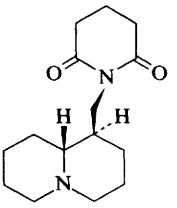
same plant has now yielded[12] *N*-methylcytisine, sophoramine, matrine, and an alkaloid of unknown structure, Alkaloid A, $C_{23}H_{26}N_4O_3$, m.p. 260 °C, $[\alpha]_D$ − 305° (EtOH). Similarly, *Leontice alberti* Regel was initially reported[13] to contain *N*-methylcytisine, and is now known[14] to contain in addition taspine, anabasine, leontine [(−)-allomatrine], matrine, and two new alkaloids, albertidine, $C_{15}H_{24}N_2O$, m.p. 70—71 °C, $[\alpha]_D^{18°}$ +33.8° (EtOH), and (+)-sophoridine, $C_{15}H_{24}N_2O$, m.p. 108—109 °C, $[\alpha]_D^{22°}$ +59.3°(H_2O).

B. Bicyclic Alkaloids.—Full details of the syntheses of lupinine and epilupinine, first reported[15] in 1960, have now been published;[16] this paper also includes the synthesis of sparteine.

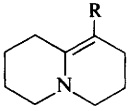
The isomerisation of (−)-lupinine (5) to (+)-epilupinine (6) has long been known to be possible by chemical methods, *e.g.* by refluxing natural (−)-lupinine in benzene with metallic sodium, but the yields are low and not consistently reproducible. A preferred method, which consistently gives yields of 20—25%, involves the photochemical isomerisation of lupinine in the presence of acetophenone as sensitiser.[17]



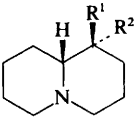
Lupinine (5, R^1 = H, R^2 = CH_2OH)
Epilupinine (6, R^1 = CH_2OH, R^2 = H)

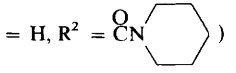


Lamprolobine (7)



(8a, R = H)
(8b, R = CO_2Et)

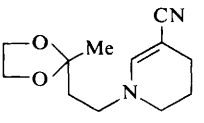


(9a, R^1 = H, R^2 = CO_2Et)
(9b, R^1 = CH_2OH, R^2 = H)
(9c, R^1 = H, R^2 = )

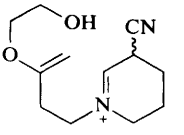
[12] I. Primukhamedov, K. A. Aslanov, and A. S. Sadykov, *Nauch. Tr., Tashkent Gos. Univ.*, 1968, No. 341, 128 (*Chem. Abs.*, 1970, **72**, 79280).
[13] S. Yunusov and L. G. Sorokina, *Zhur. obshchei Khim.*, 1949, **19**, 1955 (*Chem. Abs.*, 1950, **44**, 1997).
[14] D. Kamalitdinov, S. Iskandarov, and S. Y. Yunusov, *Khim. prirod. Soedinenii.*, 1969, **5**, 409 (*Chem. Abs.*, 1970, **72**, 75653).
[15] E. E. van Tamelen and R. L. Foltz, *J. Amer. Chem. Soc.*, 1960, **82**, 502.
[16] E. E. van Tamelen and R. L. Foltz, *J. Amer. Chem. Soc.*, 1969, **91**, 7372.
[17] S. Paszyc and H. Wróblewska, *Bull. Acad. polon. Sci., Sér. Sci. Chim.*, 1970, **18**, 15.

The structure of lamprolobine (7), from *Lamprolobium fruticosum* Benth.,[18] has now been confirmed by two independent syntheses.[19,20] The first synthesis proceeded *via* (±)-quinolizidine, which on oxidation by means of mercuric acetate gave 1,10-dehydroquinolizidine (8a). This enamine reacted with ethyl chloroformate to give ethyl 1,10-dehydrolupininate (8b), which was reduced by sodium borohydride to ethyl lupininate (9a). Base-catalysed epimerisation of (9a) followed by reduction with lithium aluminium hydride afforded (±)-epilupinine (9b), which was converted into the corresponding bromide by means of phosphorus tribromide and reacted with *N*-potassioglutarimide to give (±)-lamprolobine.[19]

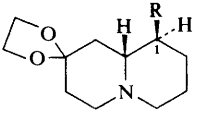
The synthesis by Wenkert and Jeffcoat[20] utilises as first stage the hydrogenation of 1-(3-oxobutyl)-3-cyanopyridinium bromide ethylene ketal, which afforded the tetrahydropyridine derivative (10). Treatment of (10) with toluene-*p*-sulphonic acid in benzene solution gave the cyanoquinolizidone ketals (12a and its C-1 epimer), presumably *via* the transient enol ether intermediate (11). Reduction ($LiAlH_4$) of (12a) and its epimer afforded the corresponding diamines, which were converted into the aminomethylquinolizidines (13a and epimer) by acid hydrolysis followed by Wolff–Kishner reduction. Finally, reaction of (13a) with glutaric anhydride gave (±)-lamprolobine (7). In confirmation of its stereochemistry, it was shown that the product (13b) of phthalation of (13a) was identical with the product obtained by appropriate transformations starting with (±)-epilupinine (6).[20]



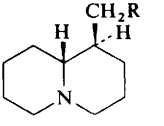
(10)



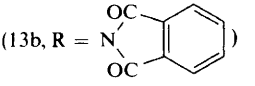
(11)



(12a, R = CN)
(12b, R = CH_2NH_2)



(13a, R = NH_2)



C. Tricyclic and Tetracyclic Alkaloids.—The chemical ionisation (C.I.) mass spectra of several quinolizidine alkaloids in the presence of methane as reactant gas have been studied;[21] the alkaloids concerned include α-isosparteine, lupanine,

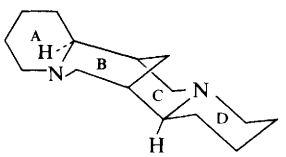
[18] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 1619.
[19] S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.*, 1970, **35**, 242.
[20] E. Wenkert and A. R. Jeffcoat, *J. Org. Chem.*, 1970, **35**, 515.
[21] H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Amer. Chem. Soc.*, 1970, **92**, 1590.

13-hydroxylupanine (14a), 13-epihydroxylupanine (14b), cytisine, angustifoline, and anagyrine. In all cases the quasi-molecular ion (QM^+) at $(M + 1)^+$ is more intense than the molecular ion in conventional electron impact (E.I.) mass spectrometry, and the pattern of fragmentation is much less complex. Further, the identification of hydroxy-groups is always possible; in 13-hydroxylupanine (14a) and 13-epihydroxylupanine (14b), for example, the ion at *m/e* 247 ($QM^+ - H_2O$) is the only major fragment ion.[21]

Following a close examination of the i.r. spectrum of β-isosparteine, and comparison with the spectra of aphylline, 17-oxosparteine, and lupanine, Skolik *et al.*[22] have deduced the conformation (15) for β-isosparteine, in which rings A and B are *cis*-fused, and rings C and D are *trans*. This conflicts with the earlier conclusion,[23] based on the n.m.r. spectrum of β-isosparteine and the reported absence of Bohlmann bands in its i.r. spectrum, that the conformation of β-isosparteine is (16). It is now claimed[22] that β-isosparteine exhibits Bohlmann bands in its i.r. spectrum, and accordingly contains at least one *trans* quinolizidine ring-junction in the molecule. The intensity of the Bohlmann bands in the 2800–2600 cm^{-1} region is interpreted as indicating the presence of only one *trans* quinolizidine ring-junction, as shown in (15). It has not yet been explained how this conclusion can be reconciled with the n.m.r. spectrum.

The two possible mono *N*-oxides of retamine, and the bis *N*-oxide, have been prepared by the perhydrol oxidation of retamine.[24] In the mono *N*-oxide-C (17) ring C is thought to have the boat conformation, and the molecule has a *trans* C–D ring-junction, since it exhibits Bohlmann bands in its i.r. spectrum. The bis *N*-oxide (18) also has a boat-shaped ring C and a *trans* C–D ring-junction, since it can be prepared by further oxidation of mono *N*-oxide-C.

The mono *N*-oxide-A does not give the bis *N*-oxide (18) on further oxidation, and is regarded as the N-16 oxide with ring C in the chair conformation.[24]



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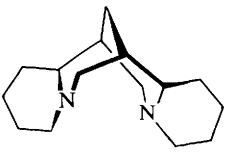

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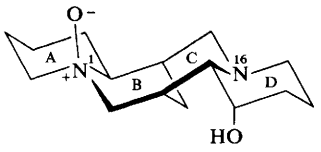
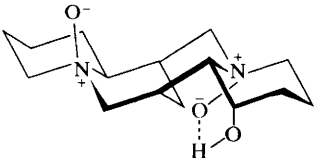


(17)

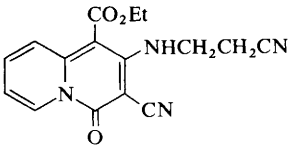


(18)

[22] J. Skolik, M. Wiewiorowski, and K. Jedrzejczak, *Bull Acad. polon. Sci., Sér. Sci. Chim.*, 1969, **17**, 201.
[23] F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, 1965, 2705.
[24] A. Pellon, R. Mosquera, L. Castedo, and I. Ribas, *Tetrahedron Letters*, 1969, 129.

A new synthesis[25] of (±)-allomatridine (19) employs the previously-prepared[26] oxoquinolizine derivative (20) as essential starting material. An attempted Thorpe cyclisation of (20) failed, but cyclisation by means of polyphosphoric acid gave the tricyclic keto-amide (21). Hydrogenation of (21) in the presence of Adams' catalyst gave a hexahydrodeoxy-derivative, whose amide function was removed by refluxing with concentrated hydrobromic acid. The product (22) reacted with ethyl acrylate in the presence of polyphosphoric acid to give the tetracyclic quinolizine derivative (23), which was finally hydrogenated to (±)-allomatridine (19) in the presence of copper chromite catalyst.[25]

Allomatridine has also been synthesised[27] by mercuric acetate oxidation of lupinoyl piperidide (9c) followed by reduction with sodium borohydride; the product was mainly racemic starting material, but a small amount (3.4%) of an isomer (24) of allomatrine was obtained, which was converted into allomatridine (19) by reduction with lithium aluminium hydride.



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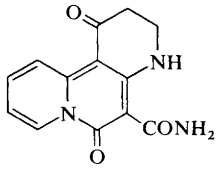

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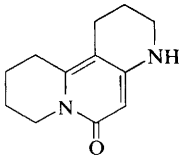

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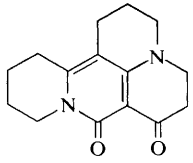

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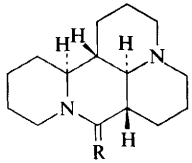


Allomatridine (19, R = H_2)
(24, R = O)

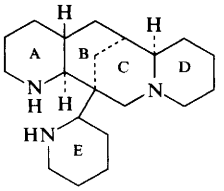
[25] G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki, and S. Matsunaga, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 124.

[26] G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *J. Pharm. Soc. Japan*, 1969, **89**, 203.

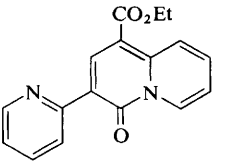
[27] T. K. Kasymov, A. I. Ishbaev, K. A. Aslanov, and A. S. Sadykov, *Khim. prirod. Soedinenii.*, 1969, **5**, 458 (*Chem. Abs.*, 1970, **72**, 67164).

2 *Ormosia* Alkaloids

The total synthesis[28] of the pentacyclic dilactam (25), which contains the complete ring-system of the *Ormosia* alkaloids, promises to afford a route to the synthesis of these alkaloids, *e.g.* piptanthine (26). The known lactam (27) was hydrogenated to a mixture of stereoisomeric octahydro-derivatives, which was converted into the keto-ester (28) by reaction with ethyl acrylate in the presence of sodium hydride. The stereochemistry of (28) was established by reduction ($LiAlH_4$) of (28a) to the corresponding hydroxy-amine, which exhibited strong Bohlmann bands in the i.r. spectrum, showing that the hydrogen at C-6 is *cis* to the C-7—C-9 bridge. Since conventional methods for the construction of ring A starting with the keto-ester (28) failed, it was treated with selenium dioxide, which gave the unsaturated keto-ester (29); this was then hydrolysed and decarboxylated to the unsaturated ketone (30). Irradiation of (30) in the presence of vinyl acetate gave a mixture of stereoisomeric acetates (31), which was brominated to a mixture of four bromoketones (32). Treatment of the crude bromoketones with sodium carbonate in aqueous methanol followed by chromatography on silica gel gave the keto-aldehyde (33); fortunately, fragmentation of the cyclobutane ring in the alternative sense was not observed. Controlled reduction [$LiAlH(OBu)_3$] of (33) gave the corresponding primary alcohol (34), which was converted *via* the mesylate into the primary chloride (35). This chloride did not react with cyanide to give the corresponding cyanide (36), hence the latter was prepared by reaction of the ethylene ketal derived from (35) with sodium cyanide and hydrolytic removal of the ketal function. Conversion of the nitrile (36) into the corresponding ethyl ester, followed by prolonged reaction of the unsaturated keto-ester (37) with ammonia, finally gave the desired lactam (25).[28]



(26)



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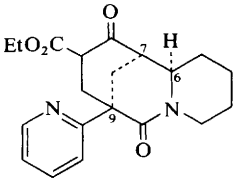
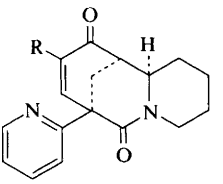
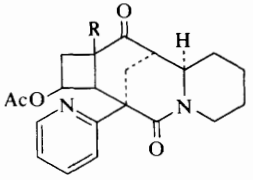


(28)
(28a; H in place of CO_2Et)

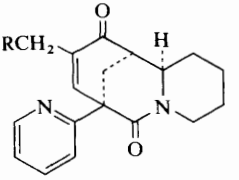


(29, R = CO_2Et)
(30, R = H)

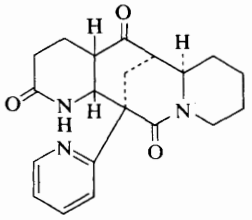
[28] H. J. Liu, Z. Valenta, J. S. Wilson, and T. T. J. Yu, *Canad. J. Chem.*, 1969, **47**, 509.



(31, R = H)
(32, R = Br)



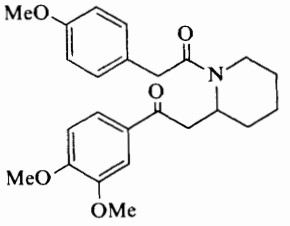
(33, R = CHO)
(34, R = CH_2OH)
(35, R = CH_2Cl)
(36, R = CH_2CN)
(37, R = CH_2CO_2Et)



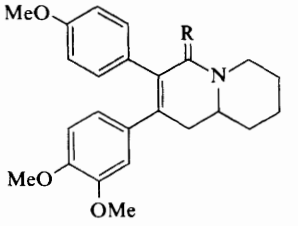
(25)

3 Cryptopleurine Group

A new synthesis of cryptopleurine (38), the phenanthroquinolizidine alkaloid of *Cryptocarya pleurosperma* White and Francis, has been described,[29] by a route which involves a biogenetically-patterned oxidative cyclisation stage. Cyclisation of the keto-amide (39) by means of potassium t-butoxide gave the quinolizidinone (40), which was hydrogenated (Pd-C–H_2) to the presumed *cis*-dihydro-derivative (41). Demethylation of (41) with boron tribromide gave the related trihydric phenol, which was successfully oxidised with manganese dioxide in the presence of silica gel to give the dienone (42); in this reaction the double bond conjugated with the amide carbonyl group was reintroduced. A mixture of acetic anhydride and sulphuric acid converted (42) into the desired triacetoxyphenanthroquinolizidinone (43, R = Ac), which was hydrolysed and methylated to the trimethyl ether (43, R = Me). Finally, reduction by lithium aluminium hydride afforded (±)-cryptopleurine (38).[29]

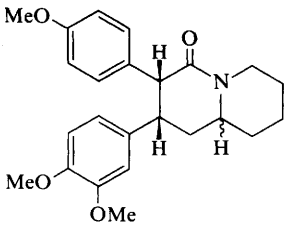


(39)

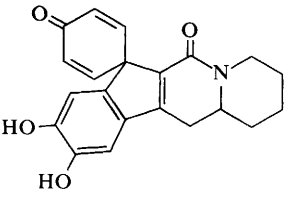


(40, R = O)
(44, R = H_2)

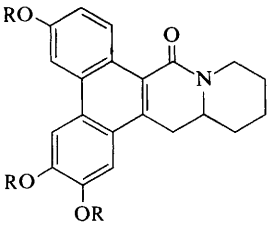
[29] J. M. Paton, P. L. Pauson, and T. S. Stevens, *J. Chem. Soc.* (*C*), 1969, 1309.



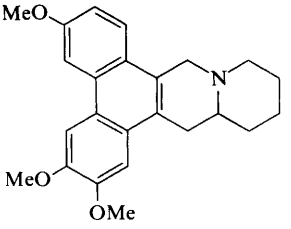
(41)



(42)



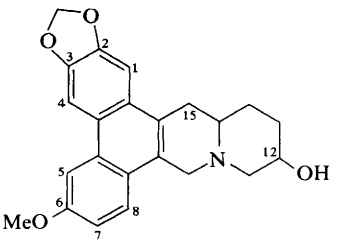
(43)



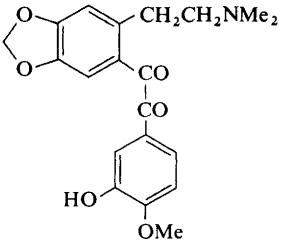
(38)

The intermediate diarylquinolizidinone (40) was also reduced by means of lithium aluminium hydride to give the related tertiary amine (44), which was shown to be identical with the *seco*-phenanthroquinolizidine alkaloid isolated from *Boehmeria platyphylla* Don.[30] The identity of the synthetic material with the natural base, for which $[\alpha]_D$ +4.6° was reported, suggests that the latter is largely racemic.[29]

A related species, *B. cylindrica* (L.) Sw., also shows cytotoxic activity, so it is of interest to note that this plant also contains cryptopleurine (38, partially racemic), the *seco*-base (44), and 3,4-dimethoxy-ω-(2′-piperidyl)acetophenone.[31] Cryptopleurine is the active principle, and it has been shown to exhibit a highly specific and potent cytotoxic activity against one particular carcinoma of the nasopharynx in cell culture.[31]



(45)



(46)

[30] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 2579.
[31] N. R. Farnsworth, N. K. Hart, S. R. Johns, J. A. Lamberton, and W. Messmer, *Austral. J. Chem.*, 1969, **22**, 1805.

Two new alkaloids, cryptopleuridine (45), m.p. 196–197 °C, $[\alpha]_D$ +90° ($CHCl_3$) and cryptopleurospermine (46), have been isolated from the bark of *Cryptocarya pleurosperma*.[32] The evidence for structure (45) for cryptopleuridine is almost entirely spectroscopic, and it should be noted that the alternative structure with the methylenedioxy-group at positions 6 and 7, and the methoxy-group at position 3, can not be excluded at present. Structure (45) is currently favoured mainly by analogy with the substitution pattern established in its congener, cryptopleurine. A second point worthy of note is the position of the axial hydroxy-group at C-12, and not at C-15 as might have been expected by analogy with the structure of tylophorinine (52; Chapter 1).

[32] S. R. Johns, J. A. Lamberton, A. A. Sioumis, and R. I. Willing, *Austral. J. Chem.*, 1970, **23**, 253.

8

Quinoline, Quinazoline, Acridone, and Related Alkaloids

BY V. A. SNIECKUS

Structural, biosynthetic, and taxonomic considerations conveniently allow for a discussion of these alkaloids under one heading.[1] A review on chromatographic methods for analysis of these alkaloids has appeared.[2]

Quinoline Alkaloids.—This section will deal with simple quinolines as well as the larger group of isopentenyl- and furo-quinolines.[3]

Continued intense investigation has supplemented the list[3b] of plant species which produce known quinoline and furoquinoline alkaloids: *Dictamnus angustifolius*,[4] *Fagara capensis* (Thunb.),[5] *F. xanthoxyloides* (*Zanthoxylum senegalense*),[6] *F. macrophylla*,[7] *Halfordia scleroxyla*,[7] *H. kendack*,[7] *Haplophyllum suaveolens* (DC) G. Don,[8] and *Monnievia trifolia*.[9] In addition, the structures of many new alkaloids have been elucidated and some of these have been synthesised. Thus, *Ailanthus giraldii* Dode[10] contains 3-isopentenyl-4-methoxy-*N*-methyl-2-quinolone, *Citrus macroptera*[11] and *Eriostemon trachyphyllus*[12] contain edulinine (1), which has been synthesised,[20] and *Echinops ritro* contains the dihydroquinoline derivative (2a).[13] *Evodia xanthoxyloides* F. Muell. has long been known to contain furoquinoline alkaloids; a more recent investigation[14] has resulted in the isolation of the epoxide (2b) of 7-isopentenyloxy-γ-fagarine and its 8-demethoxy analogue, while *Haplophyllum buchariсum*[15] contains bucharaine

[1] K. Mothes and H. R. Schütte, eds., 'Biosynthese der Alkaloide,' VEB Deutscher Verlag, Berlin, 1969, pp. 526, 551, 562; J. R. Price in 'Chemical Plant Taxonomy,' ed. T. Swain, Academic Press, London and New York, 1963, p. 429.

[2] L. Fishbein and H. L. Falk, *Chromatog. Rev.*, 1969, **11**, 1.

[3] [a] R. H. F. Manske, ed., 'The Alkaloids,' Academic Press, New York, 1970, vol. XII, pp. 456, 462, 480, 498; [b] H. T. Openshaw, *ibid.*, 1967, vol. IX, p. 223.

[4] S. A. Sultanov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 195.

[5] J. M. Calderwood, N. Finkelstein, and F. Fish, *Phytochemistry*, 1970, **9**, 675.

[6] B. A. Dadson and I. A. Mensah, *Ghana J. Sci.*, 1969, **9**, 3.

[7] W. D. Crow and J. H. Hodgkin, *Austral. J. Chem.*, 1968, **21**, 3075.

[8] M. Ionescu, I. Mester, and M. Vlassa, *Rev. Roumaine Chim.*, 1968, **13**, 1641.

[9] R. Rouffiac, I. Fouraste, and E. Stanislas, *Planta Med.*, 1969, **17**, 361.

[10] F. Bohlmann and V. S. Bhaskar Rao, *Chem. Ber.*, 1969, **102**, 1774.

[11] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1970, **23**, 419.

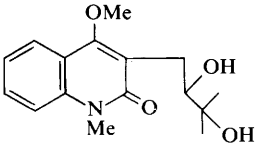
[12] E. V. Lassak and J. T. Pinhey, *Austral. J. Chem.*, 1969, **22**, 2175.

[13] W. Doepke and G. Fritsch, *Pharmazie*, 1969, **24**, 782.

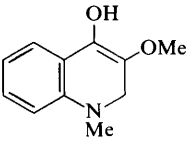
[14] D. L. Dreyer, *J. Org. Chem.*, 1970, **35**, 2420.

[15] S. M. Sharafutdinova and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 394 (*Chem. Abs.*, 1970, **72**, 67152); Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov, *ibid.*, p. 455 (*Chem. Abs.*, 1970, **72**, 79267).

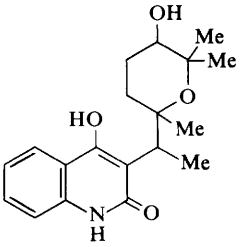
(3a) and bucharidine (3b). A number of *N*-methyl-2-quinolone derivatives, *e.g.* (4a—d), have been isolated from *Ptelea trifoliata*,[16—18] and *P. aptera* has yielded 7-isopentenyloxy-γ-fagarine (4e).[16] *Ruta graveolens*[19] has been shown to contain ribalinidine (5), together with *N*-methylplatydesminium salt (6a); the latter also occurs in *Skimmia japonica*.[20] Finally, *Ravenia* (*Lemonia*) *spectabilis*[21] contains spectabiline (6b) [not to be confused with the pyrrolizidine alkaloid (*q.v.*) of the same name]. Among these, the isolation of (4) and (5) may have special biogenetic importance.



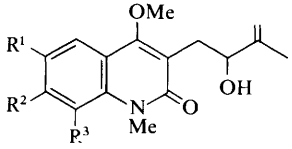
(1)



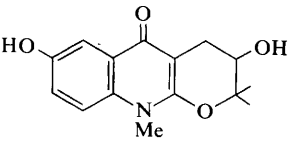
(2a)



(3b)

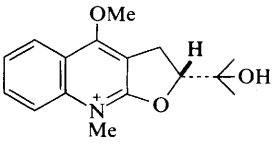


(4)

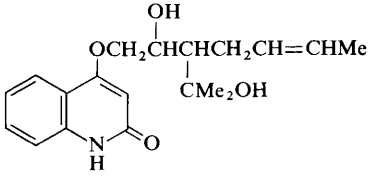


(5)

Ptelefoline (4a, $R^1 = R^3 = OMe$, $R^2 = H$)
Ptelefructine (4b, $R^1R^2 = OCH_2O$, $R^3 = OMe$)
Isoptelefoline (4c, $R^1 = H$, $R^2 = R^3 = OMe$)
Ptelefolidine (4d, $R^1 = H$, $R^2R^3 = OCH_2O$)

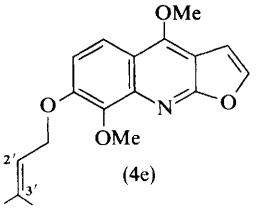


(6a)



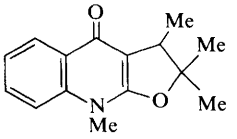
(3a)

[16] D. L. Dreyer, *Phytochemistry*, 1969, **8**, 1013.
[17] J. Reisch, K. Szendrei, V. Papay, E. Minker, and I. Novak, *Tetrahedron Letters*, 1970, 1945.
[18] J. Reisch, K. Szendrei, I. Novak, E. Minker, and V. Papay, *Tetrahedron Letters*, 1969, 3803.
[19] [a] K. Szendrei, J. Reisch, E. Minker, and I. Novak, *Herba Hung.*, 1969, **8**, 133; [b] K. Szendrei, E. Minker, M. Koltai, J. Reisch, I. Novak, and G. Buzas, *Acta Pharm. Hung.*, 1969, **39**, 60; [c] J. Reisch, K. Szendrei, E. Minker, and I. Novak, *Pharmazie*, 1969, **24**, 699 (*Chem. Abs.*, 1970, **72**, 87162).
[20] D. R. Boyd and M. F. Grundon, *J. Chem. Soc.* (*C*), 1970, 556.
[21] [a] S. K. Talapatra, B. C. Maiti, B. Talapatra, and B. C. Das, *Tetrahedron Letters*, 1969, 4789; [b] B. D. Paul and P. K. Bose, *Indian J. Chem.*, 1969, **7**, 678.

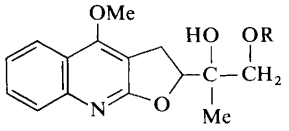


(4e)

(2b : 2′, 3′-epoxide)

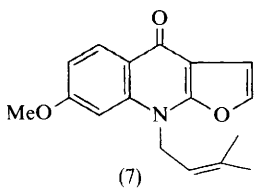


(6b)

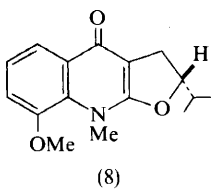


(6c), R = H
(6d), R = Ac

A quantitative method for determination of acronycine, an acridone alkaloid with antitumour activity, has been developed.[22] The constitutions of dubinidine (6c) and dubinine (6d), which have been previously discussed,[3b] have been further clarified.[23] Details of the structural elucidation[24] and extensive mass spectral studies[25] of acrophylline (7) and related alkaloids by use of deuterium and ^{18}O labelling studies have become available. Assignment of absolute configuration for some quinoline alkaloids has been announced.[26] (+)-Balfourodine (8), (−)-balfoulorone (9), and (−)-isobalfourodine (10), prepared by asymmetric synthesis, were subjected to ozonolysis followed by oxidation with hydrogen peroxide. Alkaloids (8) and (9) yielded (+)-lactone (11), while (10) afforded the (−)-lactone (12). The (+)-lactone (11) was also obtained by carrying out the same degradation on *N*-methylplatydesminium salt (6a) and its absolute configuration was established by asymmetric synthesis of its formate ester and correlated with a molecule of known configuration. The absolute configurations are thus assigned as shown: (+)-(*R*)-platydesminium methoperchlorate (6a), (+)-(*R*)-balfourodine (8), (−)-(*R*)-balfourolone (9) and (−)-(*S*)-isobalfourodine (10). A related study using the same degradative method has shown[27] that the base-catalysed isomerisation of (+)-(*R*)-balfourodine (8) to (−)-(*S*)-ψ-isobalfourodine (13) does not proceed by a previously proposed mechanism which leaves chiral centres unaffected, but involves two inversion steps *via* the epoxide (15) which equilibrates with (+)-(*R*)-ψ-balfourodine (14). The latter is converted into the thermo-



(7)



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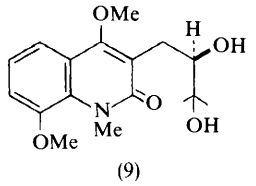
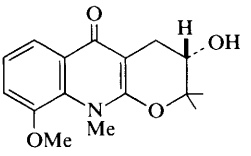


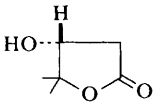
(9)

[22] F. E. Gainer and W. A. Arnett, *J. Pharm. Sci.*, 1969, **58**, 1548.
[23] I. A. Bessonova and S. Yu Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 29; *Chem. Abs.*, 1969, **71**, 3523.
[24] F. N. Lahey, M. McCamish, and T. McEwan, *Austral. J. Chem.*, 1969, **22**, 447.
[25] F. N. Lahey, I. Lauder, and M. McCamish, *Austral. J. Chem.*, 1969, **22**, 431.
[26] J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 1078.
[27] M. F. Grundon and K. J. James, *Chem. Comm.*, 1970, 337.

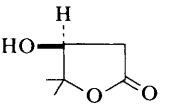
dynamically more stable compound (13). The epoxide was trapped as its *O*-methyl ether by carrying out the isomerisation in the presence of methyl iodide.



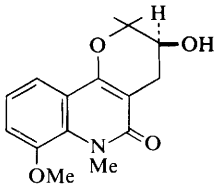
(10)



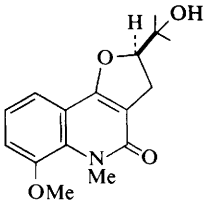
(11)



(12)



(13)



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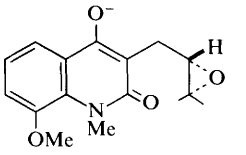

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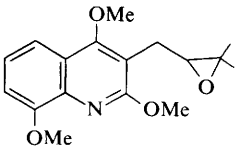
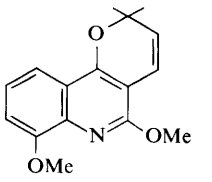


(16)



(17)

In the realm of synthesis the earlier biogenetically-patterned work of the Irish school is brought to attention.[28] Some new syntheses follow conventional lines,[29] while an attempt to use a diazomethane homologation reaction on 3-isobutyryl-4-hydroxy-8-methoxy-2-quinolone to produce lunacrine alkaloids was largely unsuccessful.[30] Two neat oxidative interconversions of furoquinoline alkaloids have been reported.[31,32]

Flindersine (17) has been prepared in one step from the isopentenylquinoline epoxide (16).[33] Several intermediates in this transformation have been isolated.

An easy synthesis of kynurenic acid has been described.[34]

[28] T. R. Chamberlain and M. F. Grundon, *Tetrahedron Letters*, 1969, 3457; for a related review, see B. J. Thyagarajan in 'Advances in Heterocyclic Chemistry,' ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1967, vol. 8, p. 143.

[29] Y. Kuwayama, T. Ota, T. Mikata, and H. Kanda, *J. Pharm. Soc. Japan*, 1968, **88**, 1050; T. Kappe, H. Schmidt, and E. Ziegler, *Z. Naturforsch.*, 1970, **25b**, 328.

[30] J. W. Huffman and J. H. Cecil, *J. Org. Chem.*, 1969, **34**, 2183.

[31] F. Piozzi, P. Venturella, and A. Bellino, *Gazetta*, 1969, **99**, 711.

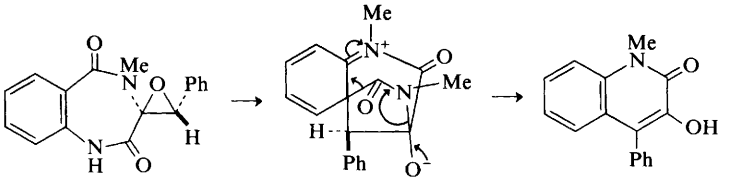
[32] J. A. Diment, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1969, **22**, 1797.

[33] R. M. Bowman, M. F. Grundon, and K. J. James, *Chem. Comm.*, 1970, 666.

[34] C. Jordanides, *Annalen*, 1969, **729**, 244.

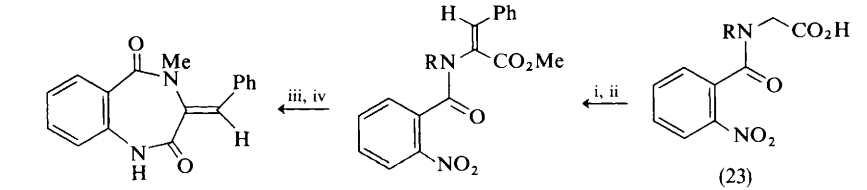
Quinazoline Alkaloids*.—A timely review on this subject has appeared.[35] Recent information is limited to isolation[36] and synthetic[37] studies.

The structural and stereochemical factors involved in the facile acid-catalysed rearrangement of cyclopenin (18) to viridicatin (20) have been determined.[38] This transformation also proceeds thermally (with the formation of methyl isocyanate) and in alkaline solution. A tricyclic intermediate (19) has been proposed for the thermal reaction and it has been shown that the benzodiazepine ring and an unalkylated amide are necessary for the rearrangement but that the epoxide ring of (18) is not a requirement.



(18) (19) (20)

Two syntheses of cyclopenin have been fully described.[39,40] One involved the preparation of a penultimate intermediate (21) as a mixture of two double bond isomers which were separated and transformed by epoxidation with *meta*-chloroperbenzoic acid into cyclopenin (18) and isocyclopenin respectively.[39] In the other, the same intermediate (21) was prepared by two stereospecific routes starting with hippuric acid derivatives (23).[40] The Erlenmeyer synthesis on (23) produced the ester (22) which gave the benzodiazepine (21) in two steps. An extension of this approach led to the synthesis of cyclopenol [(18), *m*-HOC_6H_4 for Ph].



(21) (22) (23)

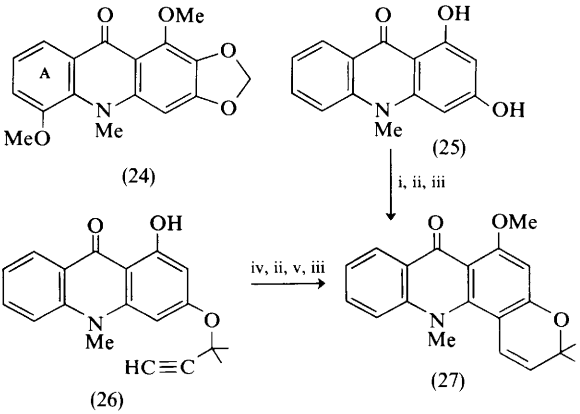
Reagents: i, PhCHO, Ac_2O, H_2SO_4; ii, MeOH; iii, Pd–C, H_2; iv, xylene, reflux.

[35] S. Johne and D. Groeger, *Pharmazie*, 1970, **25**, 22.
[36] Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 456.
[37] E. Ziegler, W. Steiger, and T. Kappe, *Monatsh.*, 1969, **100**, 948; M. Fishman and P. A. Cruickshank, *J. Medicin. Chem.*, 1970, **13**, 155.
[38] H. W. Smith and H. Rapoport, *J. Amer. Chem. Soc.*, 1969, **91**, 6083.
[39] P. K. Martin, H. Rapoport, H. W. Smith, and J. L. Wong, *J. Org. Chem.*, 1969, **34**, 1359.
[40] J. D. White, W. E. Haefliger, and M. J. Dimsdale, *Tetrahedron*, 1970, **26**, 233.

* Including cyclopenin and related structures.

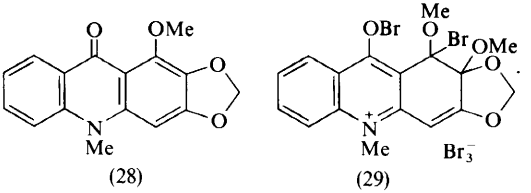
Acridone Alkaloids.—No general review on this group has appeared for at least five years, but discoveries of individual alkaloids have been recorded[41] and a discussion of antitumour properties of certain bases has been published.[42] Alkaloids have been isolated from *Acronychia baueri* (*Bauerella australiana*),[43] *A. haplophylla*,[24] *Haplophyllum dubium*,[44] and *Teclea natalensis*.[45] With the exception of *T. natalensis*, which has yielded the first known acridone type with oxygenation in ring A (24), all other plant species have been shown to contain known alkaloids.

New synthetic work in this area has been limited to two reports,[46,47] one of which involved the preparation of acronycine (27) by two equally attractive routes from the acridone derivatives (25) and (26) respectively.[47]



Reagents: i, $Me_2C(Cl)C{\equiv}CH$, K_2CO_3, NaI, DMF; ii, $PhNEt_2$, reflux; iii, Me_2SO_4, K_2CO_3, DMF; iv, Pd, $BaSO_4$; v, chloranil.

New information concerning the facile bromine addition to electron-rich acridones has appeared.[48] For example, the bromination of evoxanthine (28)



[41] R. H. F. Manske, ed., 'The Alkaloids,' Academic Press, New York, 1970, vol. XII, p. 478.
[42] G. H. Svoboda, *Ann. Reports Medicin. Chem.*, 1967, 358.
[43] H. H. S. Fong, N. R. Farnsworth, and G. H. Svoboda, *Lloydia*, 1969, **32**, 110.
[44] S. A. Sultanov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 131.
[45] K. H. Pegel and W. G. Wright, *J. Chem. Soc.* (*C*), 1969, 2327.
[46] M. Ionescu and I. Mester, *Rev. Roumaine Chim.*, 1969, **14**, 789.
[47] J. Hlubucek, E. Ritchie, and W. C. Taylor, *Chem. and Ind.*, 1969, 1809.
[48] R. H. Prager and H. M. Thredgold, *Austral. J. Chem.*, 1969, **22**, 1477, 1493, 1503, 1511.

yielded the salt (29). The mechanism of these reactions is discussed in terms of intermediacy of bromonium ions. The importance of the relief of ring-strain by the observed addition across an aromatic double-bond is noted.

9

β-Phenethylamines and Simple Isoquinoline Alkaloids

BY V. A. SNIECKUS

This section is concerned with β-phenethylamines,[1] simple isoquinolines,[2] (including 1-phenylisoquinolines) and the Ipecacuanha alkaloids.[3]

Possibly as a result of the social implications of the hallucinogenic β-phenethylamines and simple isoquinoline alkaloids, a large number of new plant species suspected to contain these structural types have been closely scrutinized with the aid of sensitive analytical methods. Thus, extensive screening of a large variety of cactus species has been carried out.[4] G.c. analysis has indicated the presence of trace amounts of dimers and trimers of phenethylamine and tetrahydroisoquinoline types[4a] while combination g.c.–mass spectrometry has enabled rapid identification of alkaloids of 120 cactus species.[4c] High voltage electrophoresis has been used for quantitative alkaloid determination.[4e] Useful structural information may be obtained from the technique of chemical ionization mass spectrometry.[5]

The following plants have been examined and found to contain phenethylamine or simple isoquinoline alkaloids: *Ariocarpus fissuratus* var. *fissuratus*,[6] *A. retusus*,[7] *Cryptostylis fulva* Schltr., which contains the phenylisoquinoline derivatives (Ia—Ic),[8] *Desmodium gangeticum*,[9] *Echinocereus merkeri*,[10] *Eria jarensis*,[11] *Glycosmis cochinchinensis*,[12] *Lepidocoryphantha runyonii*,[13] *Phalaris* species,[14]

[1] H. G. Boit, 'Ergebnisse der Alkaloid Chemie bis 1960,' Akademie-Verlag, Berlin, 1961, p. 13.

[2] [a] ref. 1, p. 210; [b] T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969, p. 25.

[3] Ref. 2(*b*), p. 160.

[4] [a] S. D. Brown, J. L. Massingill, jun., and J. E. Hodgkins, *Phytochemistry*, 1968, **7**, 2031; [b] H. W. Kircher, *ibid.*, 1969, **8**, 1481; [c] S. Agurell, *Lloydia*, 1969, **32**, 206; [d] J. S. Todd, *ibid.*, 1969, **32**, 395; [e] J. M. Calderwood and F. Fish, *J. Pharm. Pharmacol.*, 1969, **21** (Suppl.), 126.

[5] H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Amer. Chem. Soc.*, 1970, **92**, 1590.

[6] J. L. McLaughlin, *Lloydia*, 1969, **32**, 392.

[7] D. L. Braga and J. L. McLaughlin, *Planta Med.*, 1969, **17**, 87.

[8] K. Leander, B. Luning, and E. Ruusa, *Acta Chem. Scand.*, 1969, **23**, 244.

[9] S. Ghosal and P. K. Banerjee, *Austral. J. Chem.*, 1969, **22**, 2029.

[10] S. Agurell, J. Lundstrom, and A. Masoud, *J. Pharm. Sci.*, 1969, **58**, 1413.

[11] K. Hedman, K. Leander, and B. Luning, *Acta Chem. Scand.*, 1969, **23**, 3261.

[12] T.-H. Yang and J. H. G. Fan, *T'ai-wan Yao Hsueh Tsa Chih*, 1966, **18**, 33 (*Chem. Abs.*, 1970, **72**, 136333e).

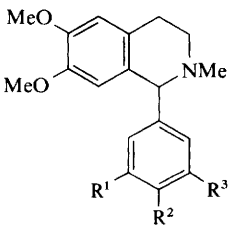
[13] S. Agurell, *Experientia*, 1969, **25**, 1132.

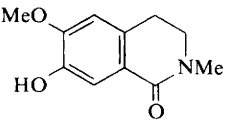
[14] R. C. S. Audette, J. Bolan, H. M. Vijayanagar, R. Bilous, and K. Clark, *J. Chromatog.*, 1969, **43**, 295.

Thalictrum minus,[15a] *T. minus* var. *adiantifolium*, which contains thalifoline (2),[15b] *Trichocereus werdermannianus* and *T. pachanoi*.[16] The peyote cactus (*Lophophora williamsii*) deserves special mention: biogenetically important mescaline derivatives have been isolated;[17] the first *N*-ethylisoquinoline alkaloid (3) has been characterised;[18] and pyrrole derivatives, *e.g.*, (4), have been identified.[19] The isolation of (4) prompted the speculation that mescaline may incorporate α-oxoglutaric acid and thus may be involved in the Krebs cycle.[19]

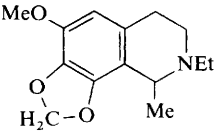
Investigation of *Allophylus cobbe*, *Homalium foetidium*, and *Aglaia* species for alkaloid content has so far yielded only simple aromatic amide derivatives.[20] An interesting phenethylamine-sesquiterpenoid alkaloid, elegantine, has been isolated from *Saussurea salsa* and *S. elegans*.[21] *NN*-Dimethylamino-*p*-hydroxyphenethylamine is the first alkaloid to be extracted from marine algae.[22]

A limited number of reports concerning the synthesis of these alkaloids have appeared.[23—29] Of these the general synthetic route *via* the transformation (5 → 6),[27a] the dehydrative cyclisation of phenethylamine oxides,[28] and the reductive decyanation of α-aminonitriles[29] deserve special mention.





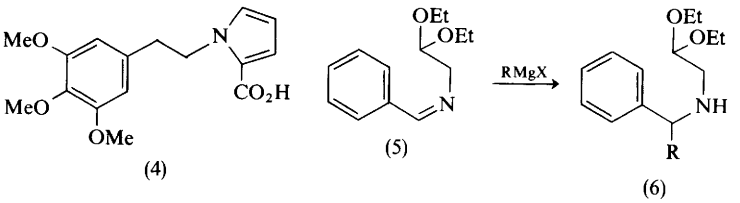
(2)



(3)

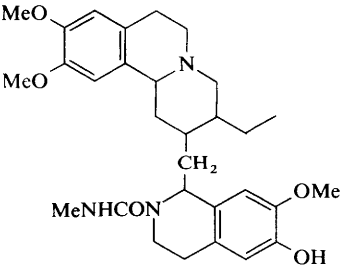
(1a), $R^1 = H$, $R^2R^3 = -O-CH_2-O-$
(1b), $R^1 = H$, $R^2 = R^3 = OMe$
(1c), $R^1 = R^2 = R^3 = OMe$

[15] [a] N. M. Mollov and H. B. Dutschewska, *Tetrahedron Letters*, 1969, 1951; [b] R. W. Doskotch, P. L. Schiff, jun., and J. L. Beal, *Tetrahedron*, 1969, **25**, 469.
[16] S. Agurell, *Lloydia*, 1969, **32**, 40.
[17] S. Agurell and J. Lundstrom, *Chem. Comm.*, 1968, 1638; G. J. Kapadia, Y. N. Vaishnav, and M. B. E. Fayez, *J. Pharm. Sci.*, 1969, **58**, 1157.
[18] G. J. Kapadia and H. M. Fales, *J. Pharm. Sci.*, 1968, **57**, 2017.
[19] G. J. Kapadia and H. M. Fales, *Chem. Comm.*, 1968, 1688.
[20] S. R. Johns and J. A. Lamberton, *Austral. J. Chem.*, 1969, **22**, 1315.
[21] A. M. Khashimov, L. S. Smirnova, S. F. Matkhalikova, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 367 (*Chem. Abs.*, 1969, **70**, 115377).
[22] K. C. Guven, A. Bora, and G. Sunam, *Eczacilik Bul.*, 1969, **11**, 177.
[23] K. Imai and Z. Tamura, *Chem. and Pharm. Bull. Japan*, 1968, **16**, 1854.
[24] E. D. Bergmann and Z. Goldschmidt, *J. Medicin. Chem.*, 1968, **11**, 1121.
[25] M. O. Abdel-Rahman, M. N. Aboul-Enein, and R. M. Taha, *J. Chem. U.A.R.*, 1968, **11**, 401.
[26] S. Teitel and A. Brossi, *J. Medicin. Chem.*, 1970, **13**, 333.
[27] [a] J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgraber, and S. Dutta, *J. Org. Chem.*, 1969, **34**, 2478: [b] M. Takido, K. L. Khanna, and A. G. Paul, *J. Pharm. Sci.*, 1970, **59**, 271.
[28] P. A. Bather, J. R. Lindsay Smith, R. O. C. Norman and J. S. Sadd, *Chem. Comm.*, 1969, 1116.
[29] S. Yamada and H. Akimoto, *Tetrahedron Letters*, 1969, 3105.



(4) (5) (6)

Most of the activity in the field of Ipecacuanha alkaloids has been of the synthetic nature. One new alkaloid, alangamide (7), from *Alangium lamarckii* Thw., has been identified[30] and several analytical methods for separation and quantitative determination have been reported.[31] Unexceptional routes to tubulosine and its relatives have been developed.[32,33] Details and extensions of synthetic work related to emetine have been reported and should be of general interest[34] (these investigations are discussed in greater detail in the following chapter). *N*-Chain extension of emetine with amino-acid residues has been reported.[35]



(7)

[30] S. C. Pakrashi and E. Ali, *Indian J. Chem.*, 1969, **7**, 635.
[31] M. S. Habib and K. J. Harkiss, *J. Pharm. Pharmacol.*, 1969, **21** (Suppl.), 57; M. Przyborowska, *Acta Pol. Pharm.*, 1969, **26**, 325.
[32] C. Szantay and G. Kalaus, *Chem. Ber.*, 1969, **102**, 2270.
[33] K. R. Williams, J. L. Kirkpatrick, B. Douglas, and J. A. Weisbach, *J. Org. Chem.*, 1969, **34**, 1572.
[34] [a] N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 85; [b] H. T. Openshaw and N. Whittaker, *ibid.*, p. 89; [c] H. T. Openshaw and N. Whittaker, *ibid.*, p. 91; [d] N. Whittaker, *ibid.*, p. 94; [e] H. T. Openshaw, N. C. Robson, and N. Whittaker, *ibid.*, p. 101.
[35] M. Nacken, P. Pachaly, and F. Zymalkowski, *Arch. Pharm.*, 1970, **303**, 122.

10

The Isoquinoline Alkaloids

BY K. W. BENTLEY

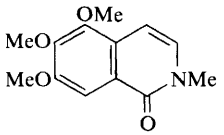
An excellent tabulated summary of the isoquinoline alkaloids, giving the structures and physical data thereof, and references to all important work on all of the alkaloids of this group known up to 1967, has recently been published.[1a] This is a work of very great value for reference.

1 Isoquinolines

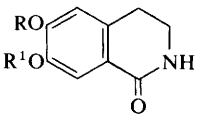
New, simple isoquinoline alkaloids isolated and assigned structures during the period under review include thalactamine (1),[1b] thalifoline (*N*-methyl derivative of 2; R = Me, R^1 = H), and noroxyhydrastinine (2; $RR^1 = CH_2$),[2] from *Thalictrum minus*, and bases of general structure (3) listed in Table 1 have been identified in Peyote.[3]

Table 1 *Alkaloids of Structure* 3

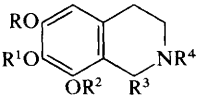
R	R^1	R^2	R^3	R^4
Me	Me	H	H	H
Me	Me	H	Me	H
Me	Me	H	H	CHO
Me	Me	H	Me	CHO
Me	Me	Me	H	CHO
Me	Me	Me	Me	CHO
Me	Me	H	H	Ac
Me	$-CH_2-$		Me	H
Me	$-CH_2-$		Me	CHO
Me	$-CH_2-$		Me	Ac
Me	$-CH_2-$		Me	Et



(1)



(2)

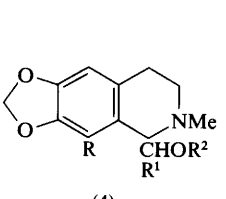


(3)

[1] [a] T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa Publishing Co., Tokyo; Elsevier Publishing Co., Amsterdam, London, & New York; 1969; [b] N. M. Mollov and K. L. B. Dutschewska, *Tetrahedron Letters*, 1969, 1951.

[2] R. W. Doskotch, P. L. Schiff, and J. L. Beal, *Tetrahedron*, 1969, **25**, 469.

[3] G. J. Kapadia and H. M. Fales, *Chem. Comm.*, 1968, 1688.



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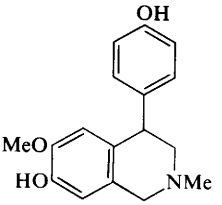


(5)

The reaction of the *pseudo*-bases cotarnine and hydrastinine with diazoalkanes R^1CHN_2 in alcoholic solution has been shown to give bases of general structure (4; R = OMe and R = H), the group OR^2 being derived from the alcoholic solvent.[4]

A newly discovered alkaloid, cherylline, has been shown to have a novel structure (5) derived from 4-phenylisoquinoline. It has been synthesised from the appropriate benzophenone by way of the alcohol, chloride, nitrile, and primary amine, followed by formylation, isoquinoline ring closure, reduction, and methylation.[5]

The biogenesis of lophocerine has been studied and the C_6–C_2–N unit shown to be derived from tyrosine; the remaining C_5 unit is derived from leucine and mevalonic acid.[6]

2 Benzylisoquinolines and the Emetine Group

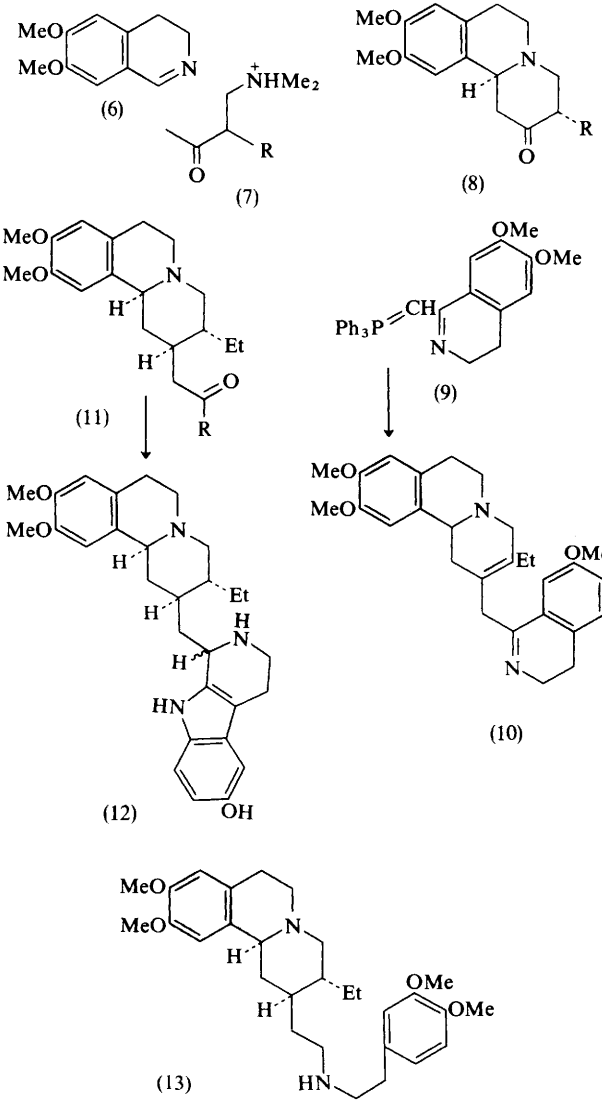
One new benzylisoquinoline alkaloid, cinnamolaurine, obtained from *Cinnamonium* species, has recently been reported. It is 1-(4-hydroxybenzyl)-6,7-methylenedioxy-2-methyltetrahydroisoquinoline, and its structure has been confirmed by synthesis.[7]

An improved synthesis of polyhydroxybenzylisoquinolines without protection of the hydroxy-groups has been reported,[8] in which Bischler–Napieralsky ring closure of the appropriate amide is achieved with phosphorus oxychloride in acetonitrile; coclaurine, isococlaurine, and reticuline, as well as a key intermediate in the synthesis of multifloramine, have been prepared in this way.

Several improvements in the synthesis of emetine and its derivatives have been reported. Condensation of the dihydroisoquinoline (6) with Mannich bases (7; R = Et, Me, H) afforded the key intermediates (8) for syntheses of emetine, C(3)-noremetine, and C(3)-bisnoremetine. Condensation of the ketone (8; R = Et) with the Wittig reagent (9) yielded 2,3-dehydro-*O*-methylpsychotrine (10) or its dihydro-compound according to the conditions.[9] The preparation of

[4] B. Goeber, S. Pfeifer, V. Hanus, and G. Engelhardt, *Arch. Pharm.*, 1968, **301**, 763.
[5] A. Brossi and S. Teitel, *Tetrahedron Letters*, 1970, 417.
[6] D. G. O'Donovan and H. Horan, *J. Chem. Soc.* (*C*), 1968, 2791.
[7] E. Gellert and R. E. Summons, *Tetrahedron Letters*, 1969, 5055.
[8] N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 85, 94.
[9] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 89.

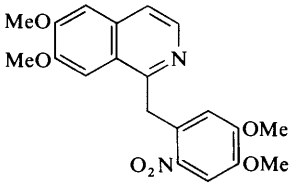
amides (11; R = NHR^1) from esters of this series has been improved,[10] and the amide obtained from the ester (11; R = OEt) and 5-hydroxytryptamine has been converted into a mixture of tubulosine and isotubulosine (12).[11,12] In the



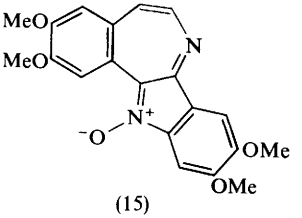
[10] H. T. Openshaw, N. C. Robson, and N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 101.
[11] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 91.
[12] C. Szantay and G. Kalaus, *Chem. Ber.*, 1969, **102**, 2270.

emetine series, appreciable amoebicidal activity has been found in the open chain amine (13).[10]

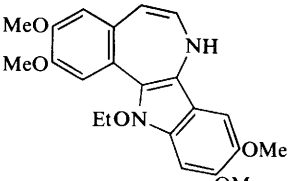
The reaction of 6′-nitropapaverine (14) with triethylphosphite has been shown to give a mixture of indolo[2,3-*a*]benzazepines (15) and (16),[13] but the same treatment of 6′-nitrolaudanosine gives only the carbazole (17),[14] and 6′-nitrolaudanosine methiodide only suffers reduction to the 6′-amino-compound.[13]



(14)



(15)



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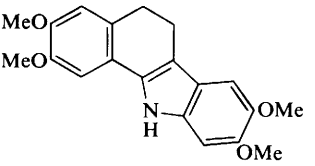
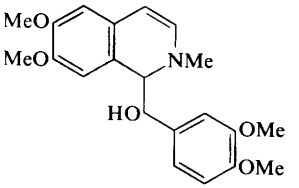
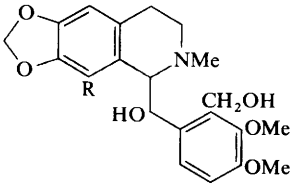


(17)

The treatment of 3,4-dehydro-9-hydroxylaudanosine (18) with 2% acetic acid on the steam bath yields veratric aldehyde and hydroxylaudanosine,[15] whereas the treatment of narcotine diol (19; R = OMe) and hydrastine diol (19; R = H) with acetic acid and tin(II) chloride yields the reduced anhydro-compounds (20; R = OMe and H).[16] The oxidation of narcotine with mercury(II) acetate and EDTA affords tarconine methyl ether (21), meconine, and opianic acid.[17]

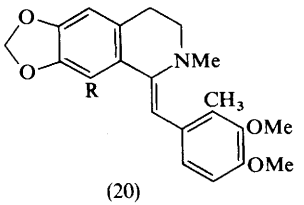


(18)

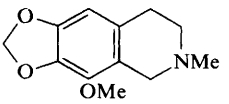


(19)

[13] T. Kametani, T. Yamanaka, K. Ogasawara, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1970, 380.
[14] T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Org. Chem.*, 1968, **33**, 4446.
[15] W. Wiegrebe and E. Roesel, *Arch. Pharm.*, 1969, **302**, 310.
[16] H. Yamaguchi, A. Numata, and N. Morita, *J. Pharm. Soc. Japan*, 1969, **89**, 869.
[17] W. Wiegrebe, E. Roesel, W. D. Sasse, and H. Kepper, *Arch. Pharm.*, 1969, **302**, 22.



(20)

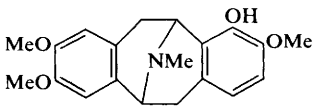


(21)

3 Pavine and Isopavine Alkaloids

A new pavine alkaloid, platycerine, from *Argemone gracilenta*, has been assigned the structure (22), [18] and an isomeric base, thalisopavine, has been isolated from *Thalictrum* species and assigned the structure (23), which was confirmed by synthesis.[19] Other isopavines, isolated from *Roemeria refracta* are reframidine (24; $RR^1 = CH_2$)[20,21] and roemrefrine, which is an isomer of reframidine with the methylenedioxy and dimethoxy groups transposed.[22] The structures were assigned on the basis of mass spectrometric studies.[21]

Since *N*-dimethoxybenzyl-4-hydroxyisoquinolines are readily cyclised in acids (24), it has been suggested that isopavine alkaloids arise from 4-hydroxybenzyl-isoquinoline bases, and in support of this view it has been found that the acetal (25) is converted in acids to amurensine (27), presumably by way of a base such



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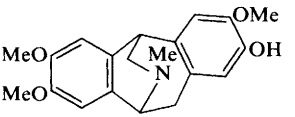

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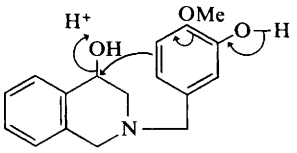

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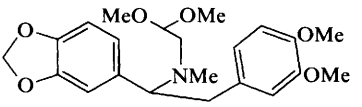
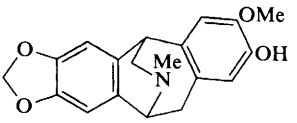
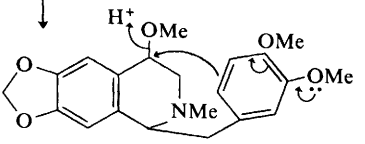


(25)



(27)



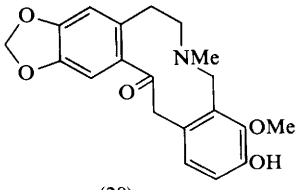
(26)

[18] F. R. Stermitz and K. D. McMurtrey, *J. Org. Chem.*, 1969, **34**, 555.
[19] S. M. Kupchan and A. Yoshitake, *J. Org. Chem.*, 1939, **34**, 1062.
[20] J. Slavik, L. Slavikova, and L. Doljes, *Coll. Czech. Chem. Comm.*, 1968, **33**, 4066.
[21] L. Doljes and J. Slavik, *Coll. Czech. Chem. Comm.*, 1968, **33**, 3917.
[22] M. S. Yunusov, S. T. Akramov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 225.

as (26), or the related 1,2-dihydroisoquinoline. Alkaloids of the pavine group could similarly arise from 3-hydroxybenzylisoquinolines.[23]

4 Berberine–Protopine Alkaloids

New alkaloids of proved structure belonging to this subgroup are thalictrisine (28),[24] from *Thalictrum simplex*, a positional isomer of hunemanine, from which it differs only in the transposition of the hydroxy- and methoxy-groups, kikemanine (29),[25] which is isomeric with corydalmine, mecambridine (30),[26] and orientalidine (31).[26,27] The last two bases, which are clearly related, are obtained from *Papaver orientale* and belong to the rare group of protoberberine structures with an additional carbon atom attached to ring D. This carbon atom was originally placed as marked with an asterisk in formula (30),[27] as in the alkaloids alborine and mecambridine, but on spectral evidence the structures were later revised to those shown;[26] a similar placing of the CH_2OH group in the two previously known bases is highly probable.



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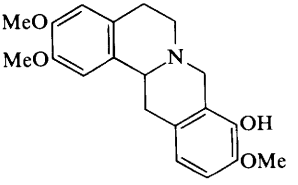

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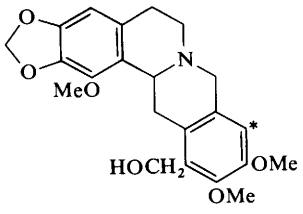

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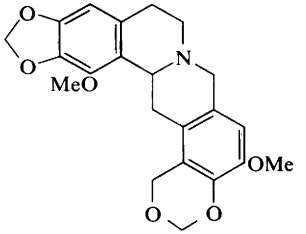
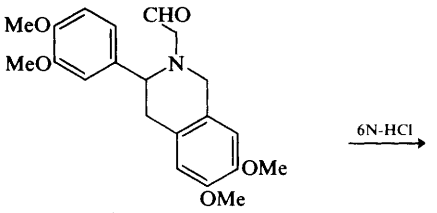


(31)

Syntheses effected in this group include a new general method whereby bases of the general type (32) are cyclised with 6N hydrochloric acid to 5-hydroxy compounds (33), which can be dehydrated and dehydrogenated to quaternary

[23] D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Letters*, 1969, 1515.
[24] Kh. S. Umarov, Z. F. Ismailov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 329.
[25] T. Kametani, M. Ihara, and T. Honda, *Chem. Comm.*, 1969, 1301.
[26] V. Preininger, V. Simanek, and F. Santavy, *Tetrahedron Letters*, 1969, 2109.
[27] V. Preininger, A. D. Cross, J. W. Murphy, F. Santavy, and T. Toube, *Coll. Czech. Chem. Comm.*, 1969, **34**, 875.

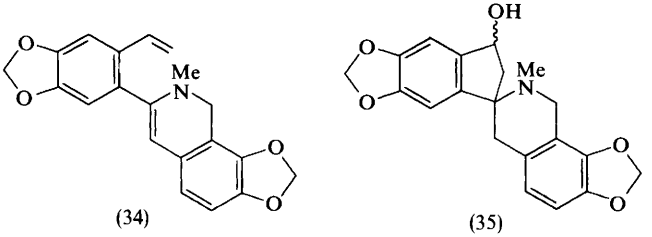
salts and then reduced with sodium borohydride. Norcoralydine has been prepared in this way,[28] and also by conventional methods.[29] Coralydine has been synthesised from 1-acetyl-2-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinolinium bromide by Bradsher's method of cyclodehydration, followed by reduction.[30] The introduction of the berberine methylene bridge into codamine was



(32) (33)

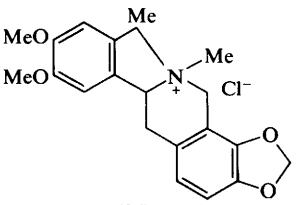
found to be effected better by formaldehyde and formic acid than by formaldehyde and hydrochloric acid,[31] and the Vilsmeier reagent (dimethylformamide and phosphorus oxychloride) has also been shown to be of use for effecting this procedure.[32] Some positional isomers of capaurimine and capauridine have been synthesised by conventional processes,[33] as has *O*-demethylstepharotine.[34]

In the protopine group anhydroprotopine (34) has been shown to be converted by hydrochloric acid into a mixture of diastereoisomeric alcohols of structure (35),[35] and the assigned structure of Perkin's ψ-cryptopine chloride has been corrected from (36) to (37),[36] which is more in accordance with what would be expected in a reaction of anhydrocryptopine methochloride with acid. Anhydroprotopine has also been converted by photolysis in benzene solution into an



(34) (35)

[28] S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Letters*, 1968, 5177.
[29] W. Meise and F. Zymalowski, *Tetrahedron Letters*, 1969, 1475.
[30] A. A. Bindra, M. S. Wadia, and N. L. Dutta, *Indian J. Chem.*, 1969, **7**, 744.
[31] T. Kametani, T. Terui, H. Agui, and K. Fukumoto, *J. Heterocyclic Chem.*, 1968, **5**, 753.
[32] Ngoc Tram Le Quang Thuan and J. Gardent, *Compt. rend.*, 1968, **267***C*, 1340.
[33] T. Kametani, H. Iida, T. Kikuchi, K. Ohkubo, and K. Fukumoto, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 1051.
[34] T. Kametani, *J. Pharm. Soc. Japan*, 1969, **89**, 721.
[35] M. Onda, K. Abe, and K. Yonezawa, *Chem. Pharm. Bull.* (*Tokyo*), 1968, **16**, 2005.
[36] S. F. Dyke and D. W. Brown, *Tetrahedron*, 1969, **25**, 5374.



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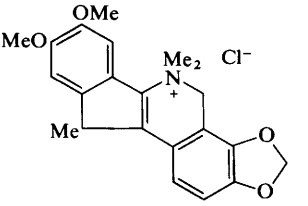
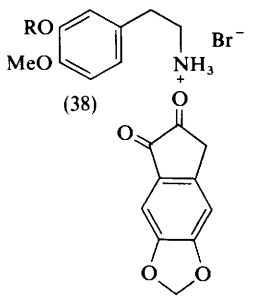


(37)

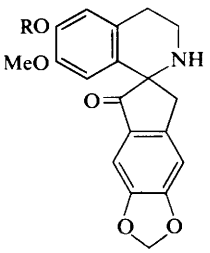
uncharacterised intermediate that yields dihydrosanguinarine on dehydrogenation over palladised charcoal,[37] thus achieving a correlation between these two groups of alkaloids, long apparent on paper, that probably is of biogenetic significance.

5 Spirobenzylisoquinolines

Several syntheses of ochotensine and related bases have been reported. The amine salts (38; R = H and R = Me) readily react with the hydrindandione (39) to give the spiro-bases (40). Of these, (40; R = Me) on treatment with an appropriate Wittig reagent gives the secondary base norochotensimine (41; R = Me), *N*-methylation of which gives ochotensimine. Protection of the hydroxy-group of the phenol (40; R = H) as the methoxymethyl ether, before the Wittig reaction, affords a route to norochotensine (41; R = H) and ochotensine.[38,39,40] An isomer[41] and analogues[42,43] of ochotensimine and the closely related alcohol fumaricine (42)[44] have been synthesised by similar methods.



(38) (39)



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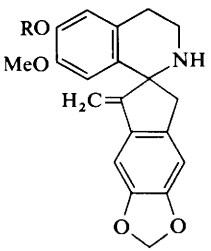

(41)

[37] M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull. (Tokyo)*, 1969, **17**, 404.
[38] H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc. (C)*, 1968, 3051.
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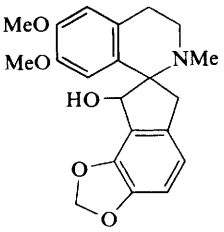

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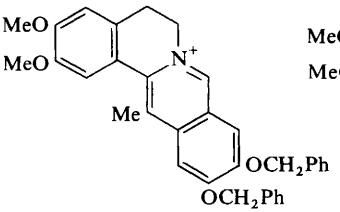

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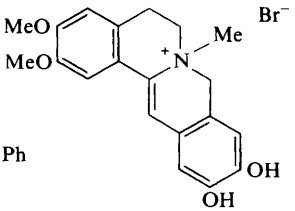
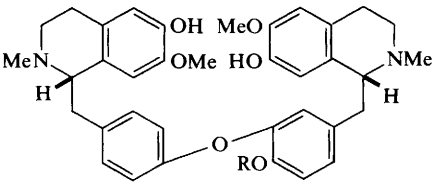


(44)

A theory of the biogenesis of the ochotensine bases from those of the berberine group has been studied and the analogue (43) of dehydrocorydaline has been reduced, *N*-methylated, and debenzylated to the salt (44), which when treated successively with sodium hydroxide, hydrochloric acid, and sodium bicarbonate, gave an analogue of ochotensimine.[45]

6 Bisbenzylisoquinolines

New alkaloids reported in the period under review include thalsimidine, which is 5-*O*-desmethylthalsimine, from *Thalictrum simplex*,[46] espinine (45; R = H) and espinidine (45; R = Me), from *Berberis laurina*,[47] penduline, which is an optical isomer of pycnamine, from *Cocculus pendulus*,[48] coclobine (46), from *Cocculus trilobus*,[49] and the mixed benzylisoquinoline–aporphine base



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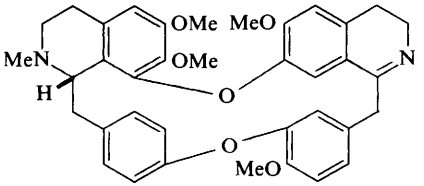

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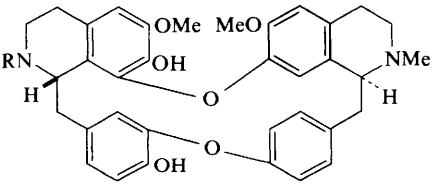
[45] M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 4009.
[46] S. Kh. Maekh, Z. F. Ismailov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 393.
[47] M. R. Falco, J. X. de Vries, Z. Maccio, and I. R. C. Bick, *Experientia*, 1969, **25**, 1236.
[48] N. C. Gupta, D. S. Bakuni, and M. M. Dhar, *Experientia*, 1970, **26**, 12.
[49] K. Ito, H. Furukawa, K. Sato, and J. Takahashi, *J. Pharm. Soc. Japan*, 1969, **89**, 1163.

adiantifoline, from *Thalictrum minus var. adiantifolium*, which is a methoxythalicarpine with the methoxy-group occupying position 7 in the aporphine nucleus.[50]

The assigned structures of some alkaloids have been corrected. Of these, thalfoetidine has been shown to be 4′-*O*-desmethylthalidasine,[51] atherospermoline to have the structure (47; R = Me) rather than (47; R = H),[52] thalmine has been shown to have the structure (48; R = H, $R^1 = R^2$ = Me) with a 5,7′ rather than an 8,7′ oxygen linkage,[53] and lauberine is a diastereoisomer of thalmine;[54] also related to thalmine are dryadine (48; R = R^1 = H, R^2 = Me) and dryadodaphnine (48; R = $R^1 = R^2$ = H).[53] Tiliacorine has been reassigned the structure (49; R = H, R^1 = Me or R = Me, R^1 = H) and tiliacorinine is a diastereoisomer;[55] in this case the linkage of the two isoquinoline nuclei through two ether linkages has been reversed.

The n.m.r. and o.r.d. spectra of berbamunine, magnoline, and their diastereoisomers have been studied, and the absolute stereochemistry of these bases assigned.[56]



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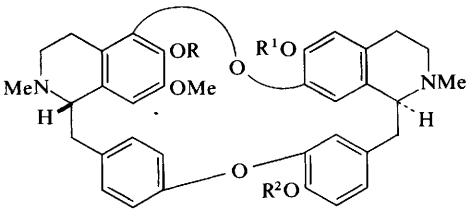

(48)

[50] R. W. Doskotch, P. L. Schiff, and J. L. Beal, *Tetrahedron Letters*, 1968, 4999.
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[52] J. Baldas, I. R. C. Bick, G. K. Douglas, and Q. N. Porter, *Austral. J. Chem.*, 1968, **21**, 2305.
[53] J. Baldas, Q. N. Porter, I. R. C. Bick, G. K. Douglas, M. R. Falco, J. X. de Vries, and S. Yu. Yunusov, *Tetrahedron Letters*, 1968, 6315.
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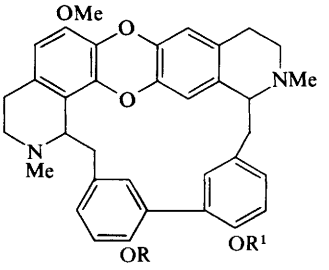
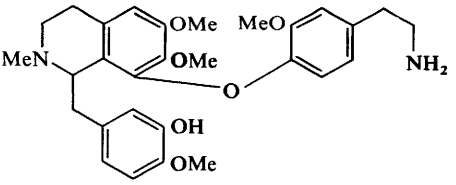
[56] T. Kametani, H. Iida, K. Sakurai, S. Kano, and M. Ihara, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 2120.



(49)

The synthesis of further bisbenzylisoquinoline alkaloids has been effected, with the Ullmann reaction being used to form the diphenyl ether linkages; bases prepared in this way include adiantifoline [from *S*-(+)-2-hydroxy-3,5,6,7-tetramethoxy-*N*-methylaporphine and *S*-(+)-6′-bromolaudanosine],[57] daurinoline,[58] magnoline and its stereoisomers,[59] and isolinearisine.[60] In a synthesis of the diastereoisomeric alkaloids phaeanthine, tetrandrine, and isotetrandrine, the bases (50) and (51) were prepared by successive Ullmann reactions and the last of these was converted into the macrocyclic lactam, which was subjected to Bischler–Napieralsky ring closure, *N*-methylation, and reduction.[61]



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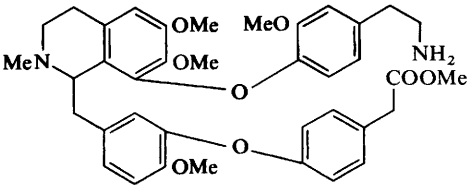

(51)

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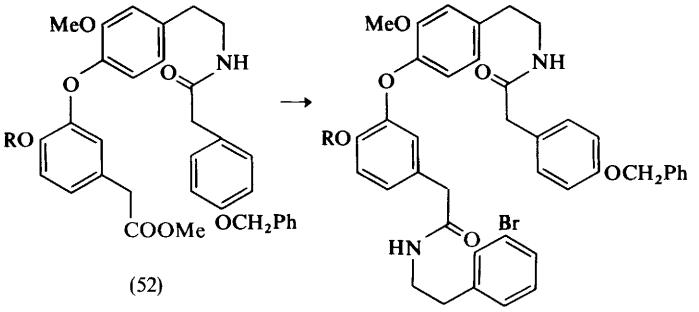
[58] T. Kametani, S. Takano, T. Kobari, H. Iida, and M. Shinbo, *Chem. Pharm. Bull.* (*Tokyo*), 1968, **16**, 1625.
[59] T. Kametani, H. Iida, and K. Sakurai, *Chem. Pharm. Bull.* (*Tokyo*), 1968, **16**, 1623; *J. Chem. Soc.* (*C*), 1969, 500.
[60] T. Kametani, S. Takano, H. Iida, and M. Shinbo, *J. Chem. Soc.* (*C*), 1969, 298.
[61] Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *J. Chem. Soc.* (*C*), 1969, 1547.

Tubocurarine iodide and its isomers have been prepared from the amide-ester (52) *via* the diamide (53), which was subjected to isoquinoline ring closure, reduction with debenzylation, Ullmann closure of the large ring, and quaternisation.[62]

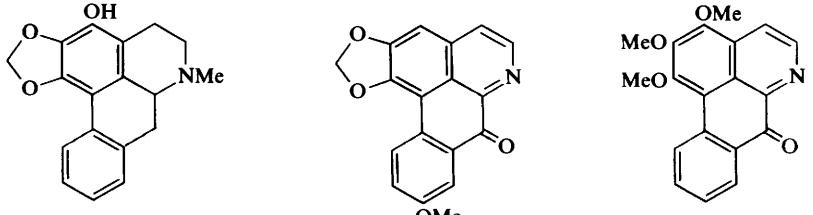


(52) (53)

(±)-*N*-Methylcoclaurine has been oxidised with horseradish peroxidase to give a bisbenzylisoquinoline with a 7,8′-diphenyl ether linkage between the two isoquinoline units, and a similar reaction occurs with lophocerine, but the same reagent oxidises (±)-armepavine (*ON*-dimethylcoclaurine) with fission and the production of *O*-methylcorypalline.[63] Quaternary *N*-methylarmepavine salts, previously said to be resistant to oxidation,[64] have been oxidised with silver nitrate and with potassium ferricyanide to give bimolecular linkage.[65]

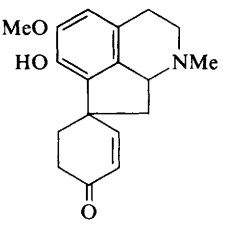
7 Aporphines and Proaporphines

Several new alkaloids of these groups have been reported. The new aporphines are steporphine (54) from *Stephania sasakii*,[66] lanuginosine (55), from *Michelia*



(54) (55) (56)

[62] V. G. Voronin, O. N. Tokkachev, A. B. Prokhorov, V. P. Chernova, and N. A. Preobrazhenskii, *Khim. geterosikl. Soedinenii*, 1969, **4**, 606.
[63] Y. Inubushi, A. Yoshiaki, and M. Michio, *Tetrahedron Letters*, 1969, 2363.
[64] B. Franck, G. Blaschke, and G. Schlingloff, *Angew. Chem. Internat. Edn.*, 1964, **3**, 192.
[65] A. M. Choudhury, I. G. C. Coutts, A. K. Durbin, K. Schofield, and D. J. Humphreys, *J. Chem. Soc.* (*C*), 1969, 2070.
[66] J. Kunimoto, Y. Okamoto, E. Yuge, and Y. Nagai, *Tetrahedron Letters*, 1969, 3287.



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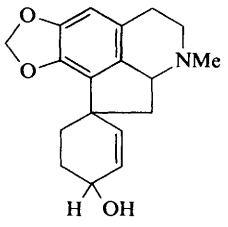

(58)

lanuginosa,[67] and imenine (56), from *Abuta imene*.[68] The new proaporphines are crotsparinine (57), from *Croton sparsifolius*,[69] and roemeronine, which is the related methylenedioxy compound, and roemeramine, the secondary alcohol (58), both from *Roemeria refracta*.[20]

Aporphine alkaloids have been synthesised by conventional methods (pukateine,[70] mecambroline,[71] domesticine,[72] and tuduranine[73]), by Pschorr cyclisation of amines prepared from nitrobenzylisoquinolines obtained from the condensation of Reissert compounds with nitrobenzyl chlorides,[74] by a new photolytic cyclisation of stilbenes to phenanthrenes, and by oxidation of benzylisoquinolines. The photolytic cyclisation is applicable to compounds of general structure (59) where R = H, Cl, or Br, and both glaucine and nuciferine have been prepared from suitable starting materials, after the appropriate modifications following cyclisation.[75] Oxidative cyclisation has been accomplished directly from suitable dihydroxybenzylisoquinolines (the nitrogen atom was protected by the CO_2Et group)[76] and *via* proaporphine bases, *e.g. N*-methylcaaverine has been prepared by the oxidation of 1-(2-hydroxybenzyl)-7-hydroxy-6-methoxy-2-methyltetrahydroisoquinoline to the ketone (60) followed by reduction to the alcohol and dienol–benzene rearrangement in acid.[77]

A total synthesis of hexahydropronuciferine has been accomplished from the nitrile (61) which on reduction, acetylation, and reaction with the Wittig reagent $Ph_3P{=}CHOMe$ gave the aldehyde (62). This, after oxidation to the acid, was

[67] S. K. Talapatra, A. Patra, and B. Talapatra, *Chem. and Ind.*, 1969, 1056.
[68] M. D. Glick, R. E. Cook, M. P. Cava, M. Srinivasan, J. Kunimoto, and A. I. DaRocha, *J. Chem. Soc.* (*C*), 1969, 1217.
[69] D. S. Bhakuni and M. M. Dhar, *Experientia*, 1969, **25**, 354.
[70] F. Zymalkowski and K. H. Happel, *Chem. Ber.*, 1969, **102**, 2959.
[71] S. Narayanaswami, S. Prabhakar, and G. Shanmugasundaram, *Indian J. Chem.*, 1969, **7**, 755.
[72] T. R. Govindachari, N. Viswanathan, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 1969, **7**, 841.
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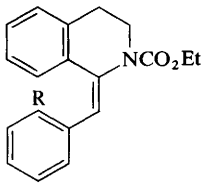
[75] M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, 1970, **35**, 175.
[76] T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, 1969, **25**, 3667.
[77] T. Kametani and I. Noguchi, *J. Chem. Soc.* (*C*), 1969, 502.



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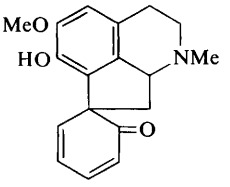

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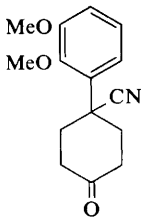

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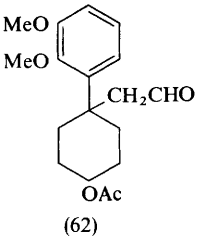

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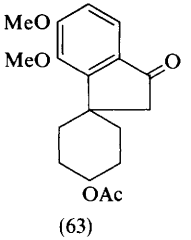
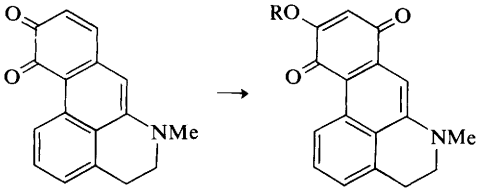


(63)

cyclised to the ketone (63), onto which the isoquinoline ring was built by methods previously reported in the literature.[78]

The absolute stereochemistry of aporphine alkaloids has been studied in relation to the substituents in ring D.[79]

The oxidation of aporphines containing phenolic hydroxy-groups has been studied. The mode of oxidation of apomorphine has been shown to be dependent



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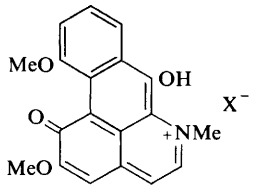

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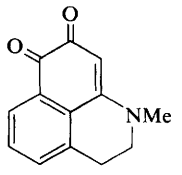


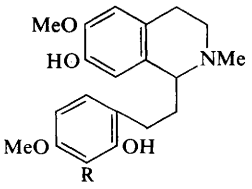
(66)

[78] J. W. Huffman and C. E. Opliger, *Tetrahedron Letters*, 1969, 5243.
[79] M. Shamma and M. J. Hillman, *Experientia*, 1969, **25**, 544.

on pH. In acidic or neutral solution this catechol derivative is oxidised to the *ortho*-quinone (64), identified by its condensation product with 3-amino-*p*-toluidine. In alkaline solution oxidation proceeds further to the quinone (65; R = H), which can be methylated to the ether (65; R = Me) and the quinone (66).[80] The oxidation of aporphines with air, iodine, or mercuric acetate has been shown to be dependent on the presence and position of hydroxy-groups, and isothebaine has been shown to give the salt (67).[81]

8 Phenethylisoquinolines and Their Derivatives

The oxidation of phenolic phenethylisoquinolines has been studied in some detail. With iron(III) chloride the bases (68; R = H and R = OMe) have been oxidised to the homoproaporphine bases (69; R = H and OMe),[82] and the base (70) has been oxidised to the homoproaporphine (71), which yielded the homoaporphine alkaloid multifloramine when subjected to dienone–phenol rearrangement.[83] In this last process, when the dienone (71) was treated with concentrated hydrochloric acid in glacial acetic acid, the mixed acetal (72; R = Me), convertible into the hemiacetal (72; R = H), was isolated.[83]



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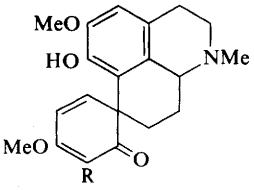
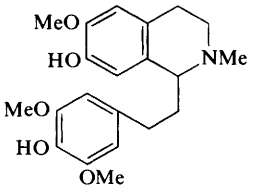
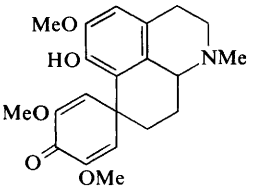


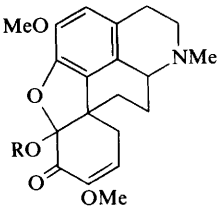
(69)



(70)



(71)

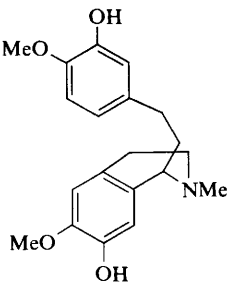


(72)

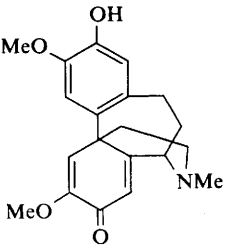
The oxidation of the diphenol (73) by chemical means gives the androcymbine analogue (74),[84] and the oxidation of the base (75) by potato peel enzymes in

[80] K. Rehse, *Naturwiss.*, 1968, **55**, 390; *Arch. Pharm.*, 1969, **302**, 487.
[81] V. Preininger, J. Hrbeck, Z. Samek, and F. Santavy, *Arch. Pharm.*, 1969, **302**, 808.
[82] T. Kametani, K. Fukumoto, T. Hayasaka, F. Satoh, and K. Kigasawa, *J. Chem. Soc.* (*C*), 1969, 4.
[83] A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 678; T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1970, 382.
[84] T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *J. Chem. Soc.* (*C*), 1969, 1295.

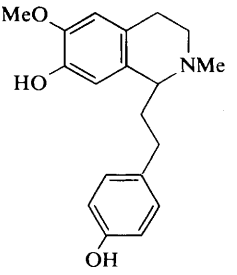
the presence of hydrogen peroxide proceeds with head to tail coupling and the production of promelanthiodine (76).[85]



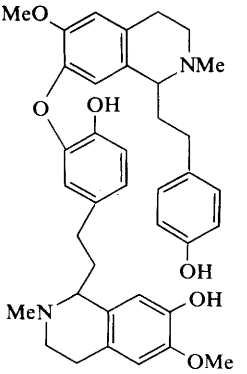
(73)



(74)



(75)

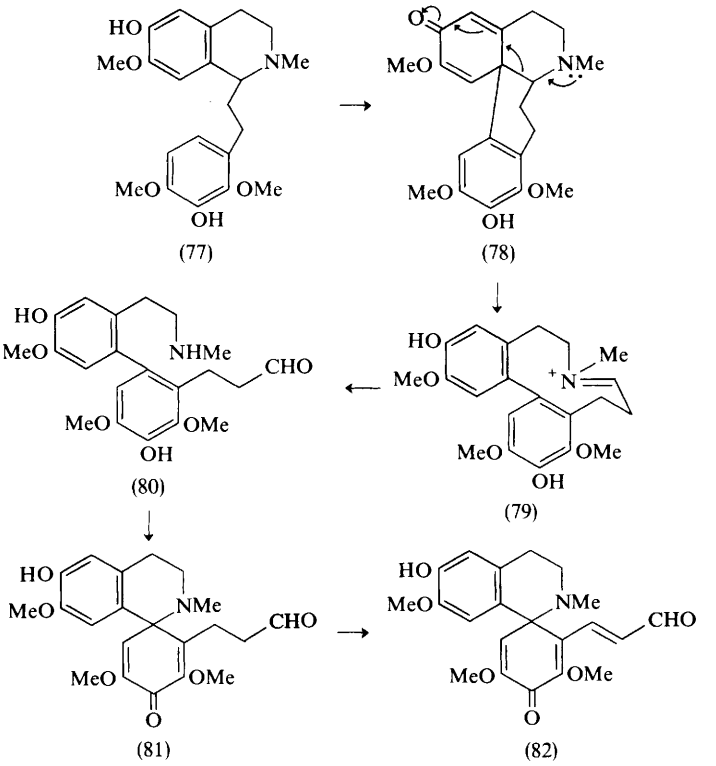


(76)

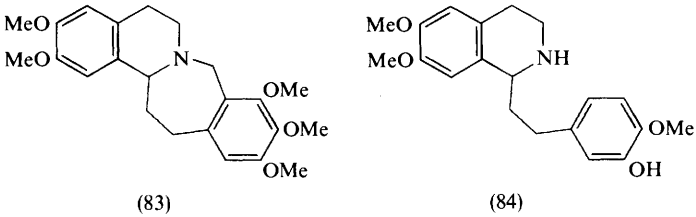
The oxidation of the base (77) with potassium ferricyanide in an attempt to obtain homoerythrina alkaloids, by way of prohomoerythrinadienone (78), resulted in the formation of β-3-hydroxy-2,4-dimethoxyphenylpropionaldehyde, 6-hydroxy-5,7-dimethoxyisoquinoline, dehydro*seco*-homoerythrinadienone (82), and the corresponding saturated aldehyde (81).[86] The last two products could well arise from the dienone (78), as shown in formulae (78)—(82).[86]

Homoprotoberberine alkaloids, *e.g.* (83), have been obtained by the condensation of secondary bases in this series with formaldehyde.[87,88] The base (84) undergoes cyclisation *ortho* to the hydroxy-group with formaldehyde and acid and *para* to the hydroxy-group under the conditions of the Mannich reaction.[89]

[85] T. Kametani, S. Takano, and T. Kobari, *J. Chem. Soc.* (*C*), 1969, 9.
[86] T. Kametani, K. Fukumoto, M. Kawatzu, and M. Fujihara, *J. Chem. Soc.* (*C*), 1970, 922.
[87] A. Brossi, A. I. Rachlin, S. Teitel, M. Shamma, and M. J. Hillman, *Experientia*, 1968, **24**, 766.
[88] A. Brossi and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 1228.
[89] T. Kametani, T. Terui, T. Ogino, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1969, 874.



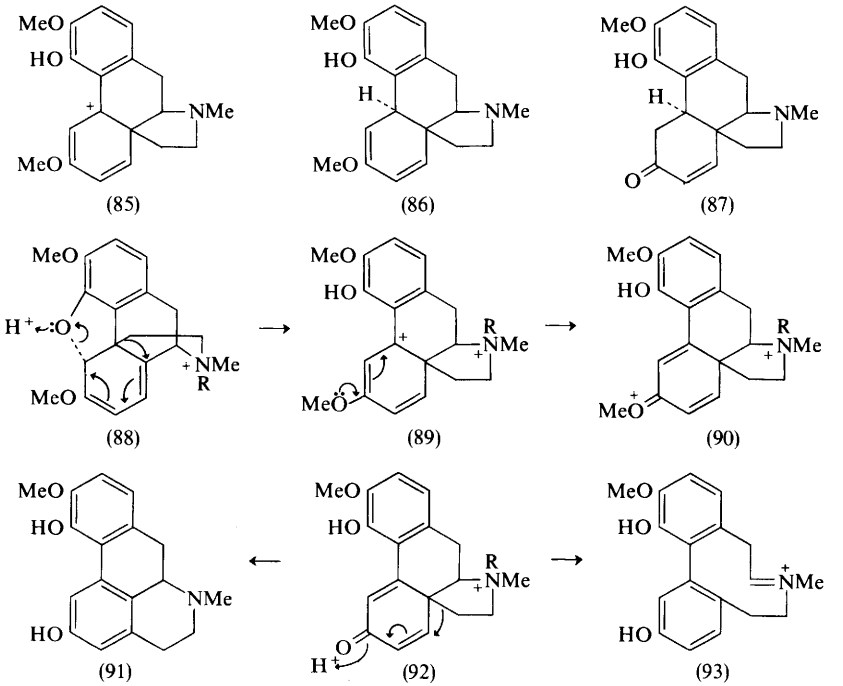
The configuration of homoproaporphines at the spiro asymmetric centre may be deduced from circular dichroism data for the bases and their derivatives.[83]



9 Morphine Group

A considerable amount of work on the alkaloids of this group has been reported.

The reduction of thebaine with lithium aluminium hydride has been re-examined, and in the presence of aluminium chloride conditions have been found to give either thebainone-A enol methyl ether or neodihydrothebaine as the main product. Also obtained was a new base, isometathebainone enol methyl ether (86), identified by hydrolysis to isometathebainone (87), which gives



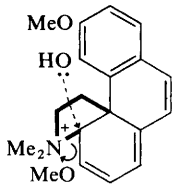
dihydrometathebainone on reduction. The enol ether (86) must arise by addition of hydride ion to the carbonium ion (85), and thebainone-A enol ether from a C-14 carbonium ion before migration of the ethanamine chain.[90]

Early suggestions that the solution of thebaine in concentrated acids contains the dienone (92)[91] have recently been confirmed. Dehydrometathebainone methoperchlorate (92; R = Me, perchlorate) has been prepared by the action of aqueous perchloric acid on thebaine methoperchlorate (88; R = Me),[92] and the unhydrolysed oxonium intermediate (90; R = Me) has been found in solutions of thebaine methotrifluoroacetate in trifluoroacetic acid. This is rapidly converted into the salt (92; R = Me) by water.[93] Thebaine in trifluoroacetic acid gives the salt (90; R = H) which rapidly gives the iminium salt (93), reducible to neodihydrothebaine.[93] The dienone is readily converted into morphothebaine (91) when the nitrogen is securely protonated and, through the salt (93), into thebenine when it is not.

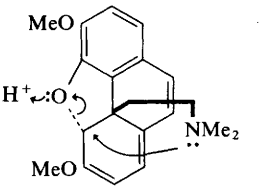
Protostephanine has recently been synthesised *via* intermediates similar in structure to these.[94]

[90] K. W. Bentley, J. W. Lewis, and J. B. Taylor, *J. Chem. Soc.* (*C*), 1969, 1945.
[91] R. Robinson, *Nature*, 1947, **160**, 815.
[92] W. Flieschhacker, R. Hloch, and F. Vieböck, *Monatsh.*, 1968, **99**, 1568.
[93] R. T. Channon, G. W. Kirby and S. R. Massey, *Chem. Comm.*, 1969, 92.
[94] A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber, and J. Staunton, *Chem. Comm.*, 1968, 1214.

Thebaine can be converted into a photo- and thermo-labile quaternary salt, thebaine cyclomethine perchlorate, containing the ion (94); the quaternary salt of the true methine base (95) has been isolated.[95]



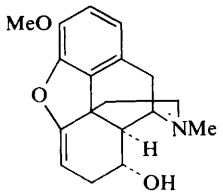
(94)



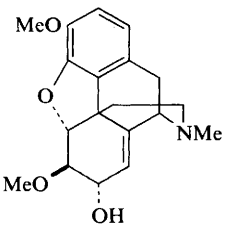
(95)

The Hofmann degradation of sinomenine methyl ether has been re-examined and an 8-methoxy-$\Delta^{8,9}$-base has been isolated. The conversion of the initial $\Delta^{7,9(14)}$-base into the $\Delta^{7,9}$-isomer results in both B/C *cis*- and *trans*-compounds.[96]

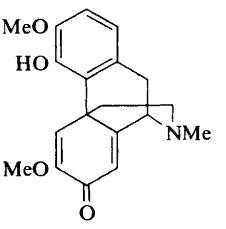
The preparation of B/C *trans*-morphine derivatives from $\Delta^{8(14)}$-compounds by hydroboration procedures followed by other transformations has been described in detail.[97,98] In this work the enol ether (96) was isolated. Previously it had been doubted whether Δ^5 compounds could exist with the oxide bridge closed, owing to the highly strained nature of the oxygen-containing ring, and C-6 ketones in the morphine series do not exchange the C-5 hydrogen for deuterium or otherwise react at C-5. Thebaine-borane with one equivalent of diborane gives the alcohol (97) and the alternative 6,7-*trans*-compound, both oxidisable to salutaridine (98), but with excess of the reagent elimination of the C-6 methoxy-group occurs in the intermediate borane.[98]



(96)



(97)

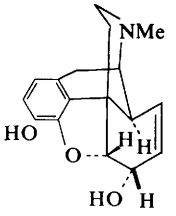


(98)

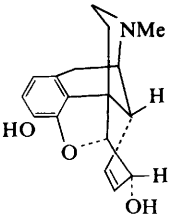
Surprise has been expressed that *trans*-morphine prepared in this way is a less potent analgesic than morphine, since isomorphinan derivatives (B/C *trans*) are more potent than derivatives of morphinan (B/C *cis*). This apparent anomaly may be explained by a consideration of the shape of the *trans*-morphine molecule,

[95] W. Flieschhacker, W. Passl, and F. Vieböck, *Monatsh.*, 1968, **99**, 300.
[96] Y. Sasaki and T. Hibino, *J. Pharm. Soc. Japan*, 1968, **88**, 1478.
[97] M. Takeda, H. Inoue, and H. Kugita, *Tetrahedron*, 1969, **25**, 1839.
[98] H. Kugita, M. Takeda, and H. Inoue, *Tetrahedron*, 1969, **25**, 1851.

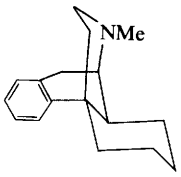
which, since it is derived from compounds containing the 4,5-oxygen bridge must be as shown in (99), with a boat-shaped ring C, and this is more similar to that of the B/C *cis*-isomer (100) than to that of isomorphinan (101). It may be noted that the 1-bromo-*trans*-dihydrocodeinone prepared by Gates and Shepard,[99] almost certainly has the structure (102) with ring C as a chair, and a *trans*-morphine prepared from this compound would be of great pharmacological interest.



(99)



(100)



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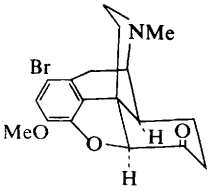
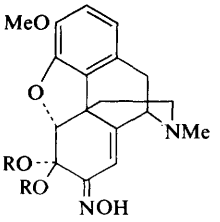


(102)

Thebaine has been shown to react with nitrosyl chloride to give the oximino-acetals (103; R = Me and Et) in methanol and ethanol respectively. The dimethyl acetal has been quaternised and subjected to Hofmann degradation.[100] β-Dihydrothebaine (104) suffers a novel closure of the oxide bridge on treatment with *p*-benzoquinone, rather than Diels–Alder addition, the product being the mixed acetal (105) which was identified by hydrolysis to quinol and codeinone.[101]

9α-Indolinocodeines (106; R = H, Ac, and Me) have been obtained by the solvolysis of 14-bromocodeine, the attack of the intermediate aziridinium salt occurring by necessity on the α-face. Of these bases (106; R = Ac) has been converted *via* the corresponding 6-chloro-compound into the base (107), the methanesulphonate of which, on solvolysis with methanolic potassium hydroxide, yields 7-methoxydeoxyneopine (108).[102,103]

[99] M. Gates and M. S. Shepard, *J. Amer. Chem. Soc.*, 1962, **84**, 4125.
[100] K. W. Bentley, G. W. Kirby, A. P. Price, and S. Singh, *Chem. Comm.*, 1969, 57.
[101] J. B. Taylor, *J. Chem. Soc.* (*C*), 1968, 1506.
[102] K. Abe, M. Onda, and S. Okuda, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 1847.
[103] K. Abe, Y. Nakamura, M. Onda, and S. Okuda, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 1917.



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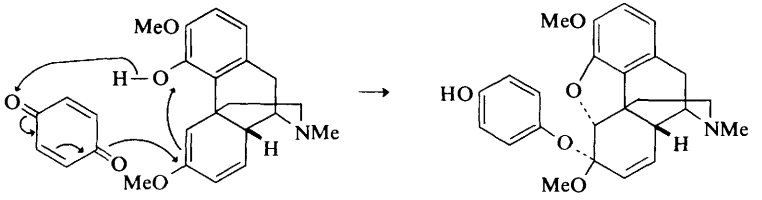
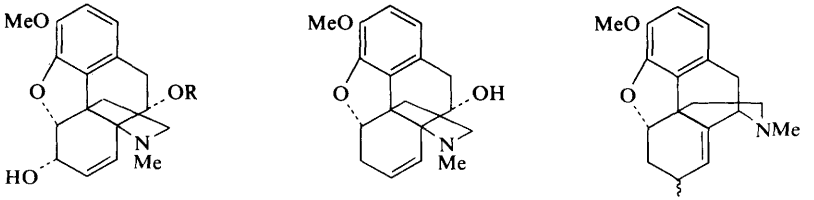
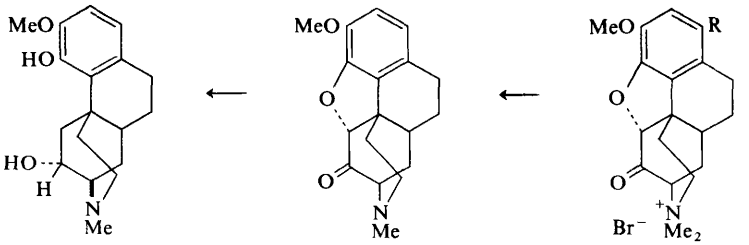


(104) (105)



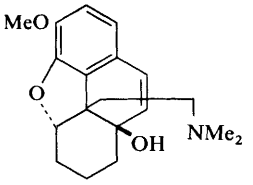
(106) (107) (108)

An isomer (110) of dihydrocodeinone has been prepared from 1,7-dibromodihydrocodeinone dihydromethine *via* the quaternary salts (111; R = Br and H). Reduction of the base (110) affords only the phenol (109), whereas the salt (111; R = H) can be reduced at the carbonyl group without opening the oxide bridge.[104]



(109) (110) (111)

[104] L. J. Sargent and B. L. Joshi, *J. Medicin. Chem.*, 1968, **11**, 336.



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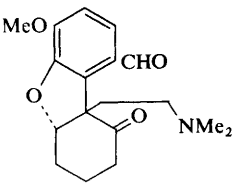

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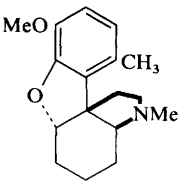
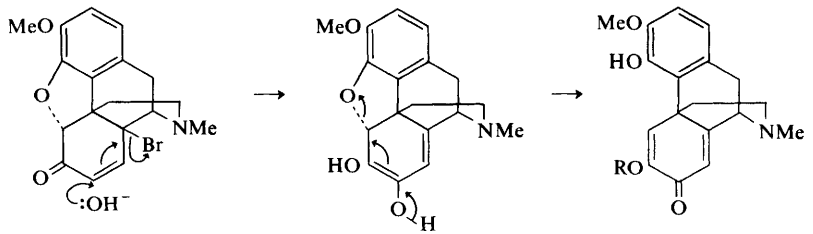


(114)

14-Hydroxydihydrodesoxycodeine methine (112) has been converted into the keto-aldehyde (113), and thence by a sequence of reactions into the octahydroindole (114), also obtainable from galanthamine, thus achieving a correlation between the two series of alkaloids.[105]

14-Bromocodeinone (115) is unstable to Claisen's alkali, which converts it, presumably through the enolised intermediate (116), into the α-diketone (117; R = H), which can be methylated to salutaridine (117; R = Me).[106] Electrolytic reduction of 14-bromocodeinone has long been known to give dihydrodeoxycodeine-E, which has recently been shown to be the phenolic $\Delta^{8,(14)}$-compound.[107]

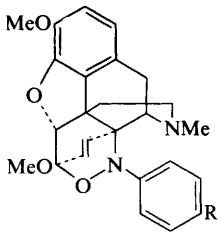


(115) (116) (117)

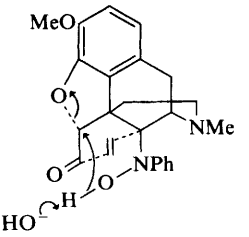
New Diels–Alder adducts of thebaine with aromatic nitroso-compounds of structure (118; R = H, Me, Cl) have been prepared. These are unstable and can be hydrolysed to 14-arylhydroxylaminocodeinones (119), which can be reduced to derivatives of the hitherto inaccessible 14-aminodihydrocodeinone (120). The base (119; R = H) is susceptible to base-catalysed displacement of the oxide bridge, the product being the 5,14-bridged thebainone derivative (121).[108]

The reaction between thebaine and excess of ethyl azodicarboxylate involves Diels–Alder addition and addition of the N-CH_3 group to a second molecule of azo-ester. The primary product (122) has not been isolated pure, but yields ethyl hydrazodicarboxylate and the substituted codeinone (123) on hydrolysis.[109]

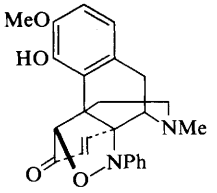
[105] M. Mokotoff and L. J. Sargent, *J. Org. Chem.*, 1968, **33**, 3551.
[106] D. E. Rearick and M. Gates, *Tetrahedron Letters*, 1970, 507.
[107] V. Weiss, T. Rüll, and R. B. Bradley, *J. Org. Chem.*, 1968, **33**, 3000.
[108] K. W. Bentley, P. Horsewood, G. W. Kirby, and S. Singh, *Chem. Comm.*, 1969, 1411.
[109] H. Merz and K.-H. Pook, *Tetrahedron*, 1970, **26**, 1727.



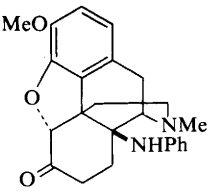
(118)



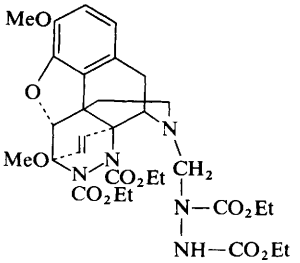
(119)



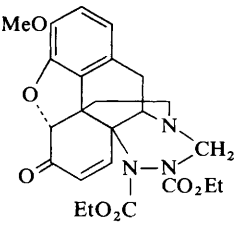
(121)



(120)



(122)



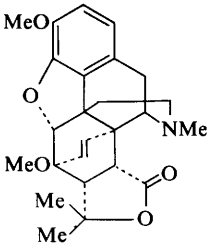
(123)

The diethyl ester derived from the Diels–Alder adduct of thebaine with maleic anhydride has been converted into the lactone (124), by methylmagnesium iodide, and into a diol by lithium aluminium hydride. The diol has been dehydrated to the diene (125), which undergoes Diels–Alder addition of *N*-phenylmaleimide to give the adduct (126).[110]

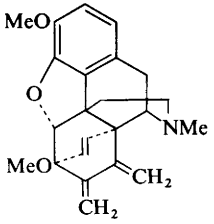
Further rearrangements of the Diels–Alder adducts of thebaine and their derivatives have been studied. Thebainequinol and one of its methyl ethers are rearranged to flavothebaone derivatives by alkalis.[111] The reaction is analogous

[110] J. W. Lewis and W. I. Rushworth, *J. Chem. Soc.* (*C*), 1970, 560.

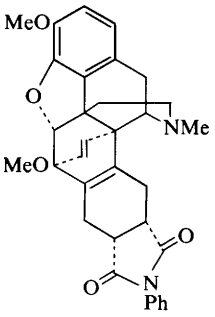
[111] Z. J. Barneis, J. D. Carr, R. J. Warnet, and D. M. S. Wheeler, *Tetrahedron*, 1968, **24**, 5053.



(124)



(125)



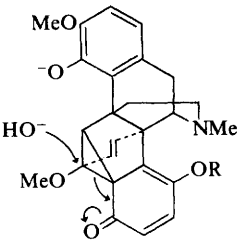
(126)

to some previously reported,[112] and presumably proceeds through the unstable intermediate (127). Dihydrothebainequinone is rearranged by bases through the intermediate (128) to the enol ether (129), which can be further transformed to dihydroflavothebaone enol methyl ether (130).[113]

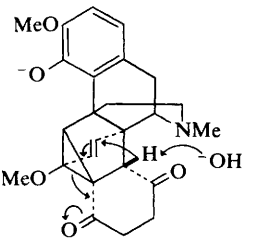
The product of photolysis of thebainequinol, previously reported to be a dimer,[114] has been shown by *X*-ray studies to have the structure (131).[115]

Branched chain alcohols in the 6,14-*endo*-ethanotetrahydrothebaine series of structure (132; R = Me or H) are readily rearranged by formic acid to tetrahydrofurans (133), which are further transformed by mineral acid into the bases (134) with the loss of the elements of water.[116] These acid-catalysed rearrangements differ markedly from those previously reported for unbranched alcohols.[117]

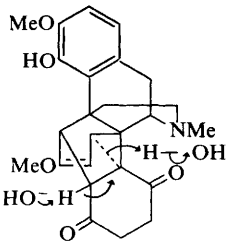
[112] K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Amer. Chem. Soc.*, 1967, **89**, 3312.
[113] K. W. Bentley and B. Meek, *J. Chem. Soc.* (*C*), 1969, 2233.
[114] Z. J. Barneis, D. M. S. Wheeler, and T. H. Kinstle, *Tetrahedron Letters*, 1965, 275.
[115] M. G. Waite, G. Sim, G. R. Olander, R. J. Warnet, and D. M. S. Wheeler, *J. Amer. Chem. Soc.*, 1969, **91**, 7765.
[116] K. W. Bentley, D. G. Hardy, B. Meek, J. B. Taylor, J. J. Brown, and G. O. Morton, *J. Chem. Soc.* (*C*), 1969, 2229.
[117] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3293.



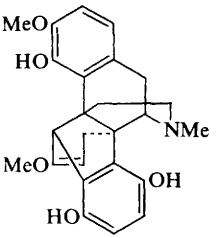
(127)



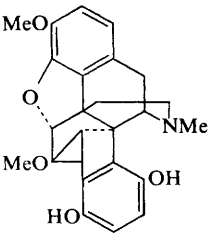
(128)



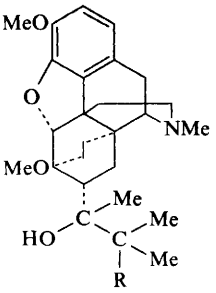
(129)



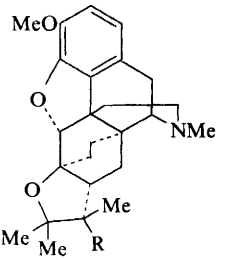
(130)



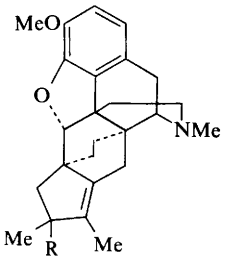
(131)



(132)

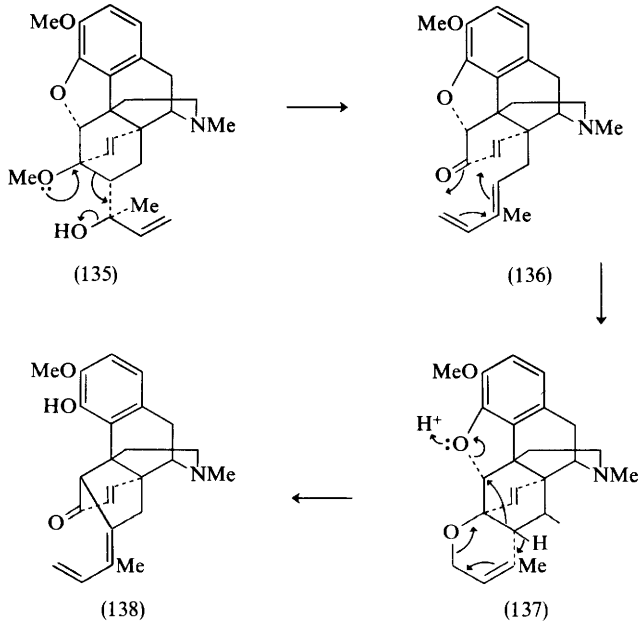


(133)



(134)

The allylic alcohol (135) is rearranged by formic acid to the ketone (136), which readily cyclises to the base (137), and this is further rearranged by mineral acid to the phenolic ketone (138).[116]

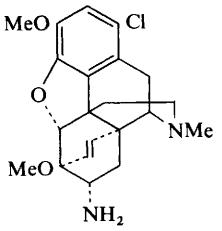


(135) (136) (138) (137)

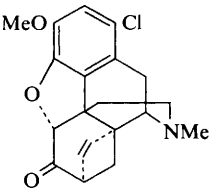
The 7-amino-compound (139) has been rearranged through the carbonium ion to the saturated ketone (140), with migration of the etheno-bridge.[118]

The base (141), unlike the corresponding 6-methoxy compound, is readily transformed by acids into characterisable compounds, and with perchloric acid gives the iminium salt (142) which can be hydrolysed to the diketone (143).

[118] K. W. Bentley, D. G. Hardy, and A. C. B. Smith, *J. Chem. Soc.* (*C*), 1969, 2235.

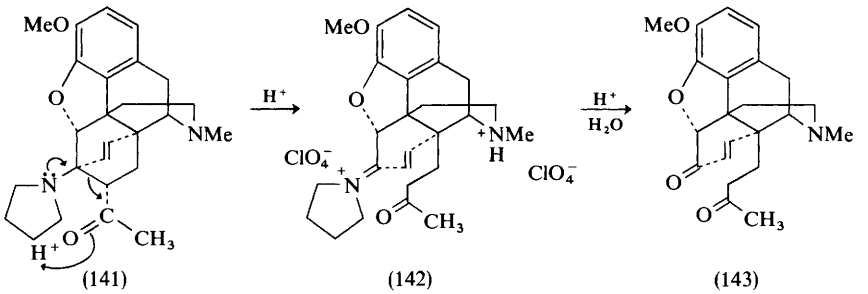


(139)



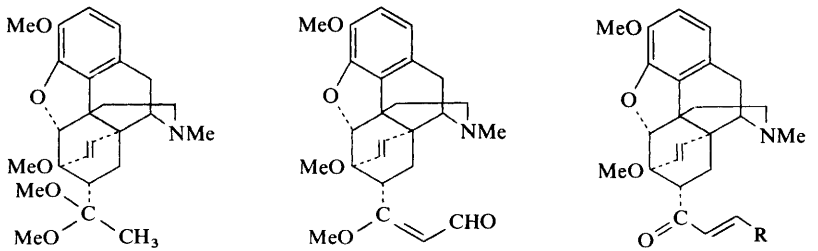
(140)

This diketone can be cyclised by hydrochloric acid to the 6-hydroxy analogue of the ketone (141).[119]



(141) (142) (143)

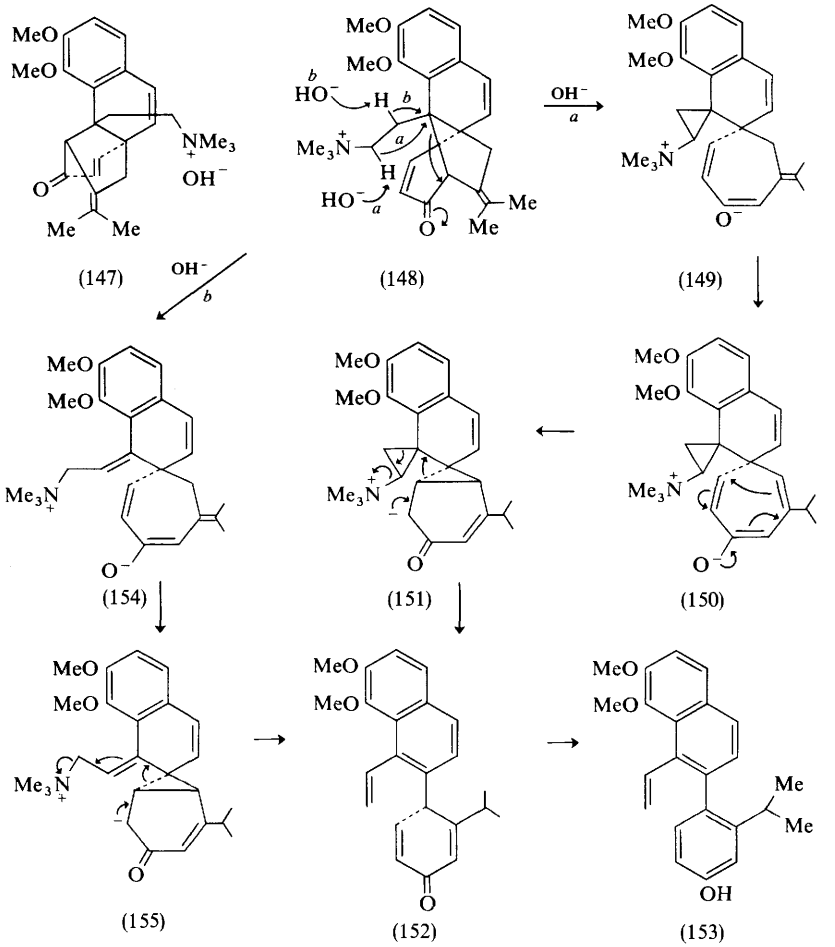
The acetal (144) has been converted by the Vilsmeier reagent into the methoxy-enal (145), from which a variety of heterocyclic compounds has been obtained.[120] The enal will condense with reactive methylene compounds, and reacts with lithium alkyls to give, after hydrolysis, $\alpha\beta$-unsaturated ketones of general structure (146); these are reducible to saturated ketones, which would otherwise be available only by Diels–Alder addition of dienophiles that are difficult to obtain, to thebaine.[121]



(144) (145) (146)

[119] J. J. Brown, R. A. Hardy, and C. T. Nora, U.S.P., 3,488,354 (1969) (*Chem. Abs.*, 1970, **72**, 79281k).
[120] J. J. Brown and R. A. Hardy, U.S.P., 3,474,102 (1969) (*Chem. Abs.*, 1970, **72**, 21816x).
[121] J. J. Brown and R. A. Hardy, U.S.P., 3,474,103 (1969) (*Chem. Abs.*, 1970, **72**, 43967z).

Other compounds of potential pharmacological interest have been prepared in the 6,14-*endo*-ethenotetrahydrothebaine series by nuclear substitution,[122] modification of the C-7 substituent,[123,124] 3,6-*O*-demethylation,[125] removal of the C-3 oxygen function,[126] and by ozonolysis.[127] The last of these reactions involves fission of the aromatic nucleus, and, surprisingly, affords compounds that still show potent analgesic activity.

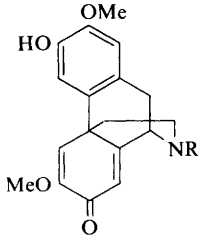


[122] K. W. Bentley, J. D. Bower, and A. C. B. Smith, *J. Chem. Soc.* (*C*), 1969, 2241.
[123] K. W. Bentley, J. D. Bower, J. W. Lewis, M. J. Readhead, A. C. B. Smith, and G. R. Young, *J. Chem. Soc.* (*C*), 1969, 2237.
[124] K. W. Bentley, D. G. Hardy, J. W. Lewis, M. J. Readhead, and W. I. Rushworth, *J. Chem. Soc.* (*C*), 1969, 826.
[125] K. W. Bentley, J. D. Bower, and J. W. Lewis, *J. Chem. Soc.* (*C*), 1969, 2569.
[126] J. W. Lewis and M. J. Readhead, *J. Medicin. Chem.*, 1970, **13**, 525.
[127] K. W. Bentley, D. G. Hardy, and P. A. Mayor, *J. Chem. Soc.* (*C*), 1969, 2385.

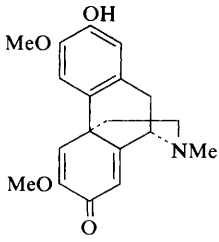
An abnormal Hofmann degradation resulting in a complex aromatisation has been observed in this series. The quaternary hydroxide (147) spontaneously decomposes to the phenol (153). Elimination of trimethylamine does not take place without rearrangement, nor rearrangement without elimination. The reaction doubtless proceeds as shown in formulae (148)—(153), with attack at the proton α to nitrogen or, *via* the intermediates (154) and (155), with attack β to nitrogen.[128]

A variety of azido- and amino-codides and morphides,[129,130] *N*-amino-normorphine,[131] and 14-hydroxycodeine[132] derivatives have been described.

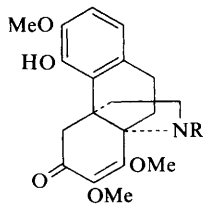
New alkaloids of this group whose structures have been assigned recently are flavinantine (156; R = Me),[133] flavinine (156; R = H),[134] pallidine (157),[135] aknadinine (158; R = Me),[136,137] aknadicine (158; R = H)[137] and aknadil-actam (159),[137] miersine (160),[138] and acutuminine (161).[139]



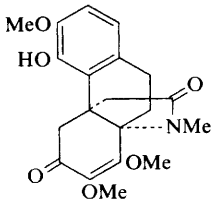
(156)



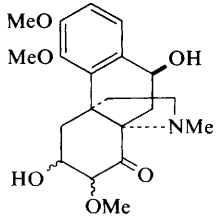
(157)



(158)



(159)



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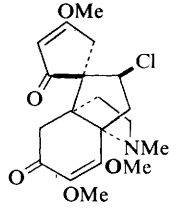
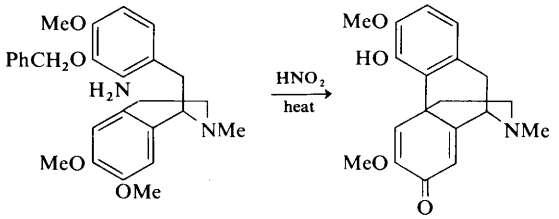


(161)

[128] K. W. Bentley, H. P. Crocker, R. Walser, W. Fulmor, and G. O. Morton, *J. Chem. Soc.* (*C*), 1969, 2225.
[129] R. Bognar and S. Makleit, *Acta Acad. Sci. Hung.*, 1968, **58**, 523; 1969, **59**, 373, 387.
[130] R. Bognar, S. Makleit, and T. Mile, *Acta Acad. Sci. Hung.*, 1969, **59**, 161, 379; *Magyar Kém. Folyóirat*, 1968, **74**, 523, 526.
[131] A. Modiri, J. G. Cannon, and S. Y. Yeh, *J. Medicin. Chem.*, 1969, **12**, 921.
[132] I. Seki and H. Takagi, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 1555.
[133] C. Chambers and K. L. Stuart, *Chem. Comm.*, 1968, 328.
[134] K. L. Stuart, C. Chambers, and D. Hyfield, *J. Chem. Soc.* (*C*), 1969, 1681.
[135] T. Kametani, M. Ihara, and T. Honda, *Chem. Comm.*, 1969, 1301.
[136] S. M. Kupchan, M. I. Suffness, D. N. J. White, I. T. McPhail, and G. A. Sim, *J. Org. Chem.*, 1968, **33**, 4529.
[137] B. K. Moza, B. Bhaduri, and D. K. Basu, *Chem. and Ind.*, 1969, 1178.
[138] A. R. Battersby, S. Ruchiwarat, J. Staunton, and C. W. Thornber, unpublished work cited by C. W. Thornber, *Phytochem.*, 1970, **9**, 157.
[139] Y. Okamoto, E. Yuge, Y. Nagai, K. Katsuta, A. Kishimoto, Y. Kobayashi, and T. Kikuchi, *Tetrahedron Letters*, 1969, 1933.

Syntheses in the morphine group recently effected include a total synthesis of (±)-salutaridine from the diazonium salt derived from the amine (162), the resolution of this to salutaridine (163) and its enantiomorph sinoacutine, and the conversion of these into (−) and (+) thebaine by known methods.[140] Since thebaine can be converted into codeine and morphine, this constitutes formal syntheses of these alkaloids. Similar syntheses have been achieved with a methylenedioxy substituent in the isoquinoline system,[141] *e.g.* those of amurine,[142] flavinantine and its methyl ether,[143,144] and an analogue of the homomorphine alkaloid androcymbine.[145] Synthesis of isosalutaridine [the antipode of pallidine (157)][146,147] and an analogue of androcymbine[148] have also been achieved by phenol oxidative coupling with potassium ferricyanide.



(162) (163)

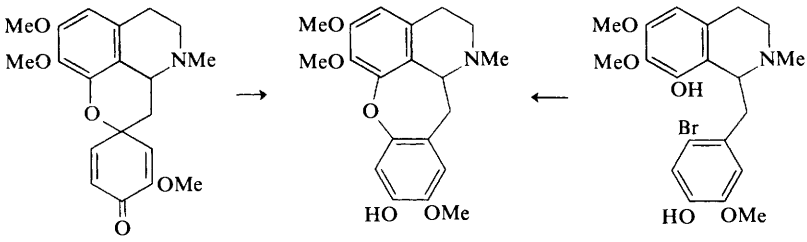
Since it is known that quaternary salts give better yields of phenolic oxidative coupling products than do tertiary bases, when oxidised with one-electron transfer agents in the laboratory, the possible role of reticuline methochloride (tembetarine chloride) in the biogenesis of more complex alkaloids has been examined. The labelled salt has been found to be very poorly incorporated into morphine, sinomenine, and protopine.[149]

10 Other Alkaloids

A possible mode of biogenesis of alkaloids of the cularine type has been simulated by the oxidation of 1-(4-hydroxy-3-methoxybenzyl)-8-hydroxy-6,7-dimethoxy-2-methyltetrahydroisoquinoline to the dienone (164), and rearrangement of this

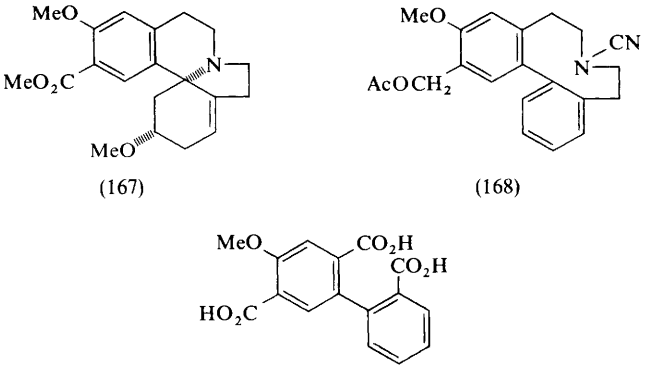
[140] T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc.* (*C*), 1969, 2030.
[141] T. Kametani, T. Sugahara, and K. Fukumoto, *Chem. and Ind.*, 1969, 833.
[142] T. Kametani, K. Fukumoto, and T. Sugahara, *J. Chem. Soc.* (*C*), 1969, 801.
[143] T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1969, 1063.
[144] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc.* (*C*), 1969, 520.
[145] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc.* (*C*), 1968, 3084.
[146] T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 2245.
[147] T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, *J. Chem. Soc.* (*C*), 1969, 2034.
[148] T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *Chem. Comm.*, 1968, 1605.
[149] D. H. R. Barton, R. B. Boar, D. A. Widdowson, V. Deulofeu, and S. M. Albonico, *J. Chem. Soc.* (*C*), 1969, 807.

in acid to the phenol (165), the structure of which was confirmed by an independent synthesis from the bromophenol (166).[150,151]



(164) (165) (166)

A new erythrina alkaloid, erythroculine, from *Cocculus laurifolius* has been shown to have the structure (167). The ester group may be reduced with lithium aluminium hydride and the acetyl ester of the resulting alcohol on treatment with cyanogen bromide affords the hindered diphenyl (168), with loss of hydrogen bromide and methanol. This on reduction to the secondary base, *N*-methylation, and successive Hofmann degradations affords an olefin that may be oxidised to the tricarboxylic acid (169).[152] The base represents a novel structure in having the additional carbon atom linked to the ring system.

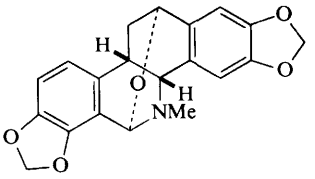


(167) (168)

(169)

In the benzophenanthridine group didehydrochelidonine has been shown to have the internal carbinolamine ether structure (170).[153] The minor alkaloids of

[150] T. Kametani, T. Kikuchi, and K. Fukumoto, *Chem. Pharm. Bull.* (*Tokyo*), 1968, **16**, 1003.
[151] T. Kametani, H. Iida, T. Kikuchi, M. Mizushima, and K. Fukumoto, *Chem. Pharm. Bull.* (*Tokyo*), 1969, **17**, 709.
[152] Y. Inubushi, H. Furukawa, and M. Ju-chi, *Tetrahedron Letters*, 1969, 153.
[153] M. H. Benn and R. E. Mitchell, *Canad. J. Chem.*, 1969, **47**, 3701.



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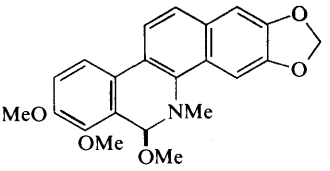
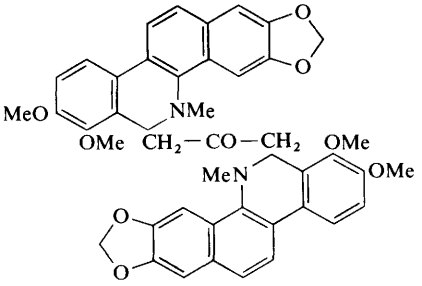


(171)



(172)

Bocconia arborea have been identified as dihydrosanguinarine, oxysanguinarine, 11-*O*-methyldihydrochelerythrine (171), and 1,3-bis-11-hydrochelerythrinylacetone (172), the structure of which was confirmed by its synthesis from chelerythrine chloride by base-catalysed condensation with acetone dicarboxylic acid.[154]

[154] D. B. McLean, D. E. F. Gracey, J. K. Saunders, R. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1969, **47**, 1951.

11

Amaryllidaceae Alkaloids

BY V. A. SNIECKUS

This group has been reviewed.[1]

Apart from the accepted structural types of this class, this report will be concerned with the mesembrane group (26), miniatine (24), and cherylline (25) because of their obvious biogenetic relationship.

Chemotaxonomic considerations of the Amaryllidaceae alkaloids have been summarized in a not widely quoted review.[2] Various chromatographic methods available for analysis of these alkaloids have been reviewed.[3]

A review on the alkaloids of the Menispermaceae includes a tabulation of the relatively few Amaryllidaceae types which are to be found in this family.[4] The following species have been shown to contain, with three exceptions, known alkaloids: *Amaryllis equistris* Ait.,[5] *Chlidanthus fragans* Herb.,[6] *Cyrtanthus mackenii* and *Cooperanthes* hybrid,[7] *Galanthus caucasicus*,[8] *Hymenocallis concinna* Baker,[9] *Sternbergia ricula*,[10] *Zephyranthes robusta*, and *Z. sulphurea*.[11] Structures for the new alkaloids have not been assigned; in one case,[6] a previously postulated structure for an alkaloid (chlidanthine; structure 102, Chapter 1) from another source[1a] has been confirmed.

After a great deal of structural uncertainty, the assignment for narcissidine has been finally resolved by *X*-ray crystallography.[12] Narcissidine is represented by (1; $R^1 = R^2 = R^3 = Me$), and on this basis the structures of several related

[1] [a] W. C. Wildman, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1968, vol. XI, p. 307; [b] T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969, p. 176.

[2] R. Hegnauer in 'Chemical Plant Taxonomy,' ed. T. Swain, Academic Press, London and New York, 1963, p. 389.

[3] L. Fishbein and H. L. Falk, *Chromatog. Rev.*, 1969, **11**, 1.

[4] C. W. Thornber, *Phytochemistry*, 1970, **9**, 157.

[5] E. V. Rao and M. N. Rao, *Current Sci.*, 1969, **38**, 291.

[6] J. G. Bhandarkar and G. W. Kirby, *J. Chem Soc.* (*C*), 1970, 1224.

[7] R. V. K. Rao, *Current Sci.*, 1970, **39**, 134.

[8] D. M. Tsakadze, T. N. Kiparenko, and N. S. Tsitsishvili, *Soobshch. Akad. Nauk Gruz. SSR*, 1969, **55**, 573; D. M. Tsakadze, A. Abdusamatov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 331; D. M. Tsakadze, T. N. Kiparenko, N. S. Tsitsishvili, A. Abdusamatov, and S. Yu. Yunusov, *Soobshch. Akad. Nauk Gruz. SSR*, 1969, **56**, 305.

[9] E. V. Rao, M. V. Devi, and R. V. K. Rao, *Current Sci.*, 1969, **38**, 341.

[10] G. Phokas, *Pharm. Acta Helv.*, 1969, **44**, 257.

[11] R. V. K. Rao, *Indian J. Pharm.*, 1969, **31**, 62; 1969, **31**, 86.

[12] J. C. Clardy, W. C. Wildman, and F. M. Hauser, *J. Amer. Chem. Soc.*, 1970, **92**, 1781.

alkaloids have been reassigned; these include parkasine (1 ; $R^1 = R^2 = Me$, $R^3 = H$) and ungiminorine (1 ; $R^1 + R^2 = CH_2$, $R^3 = H$).

A new application of the g.l.c. quantitative analysis method for tetramethylsilyl ethers of alkaloids has been reported.[13] Mass spectrometric investigations of galanthamine and related compounds continue to interest Russian workers.[14] The important technique of chemical ionization (C.I.) mass spectrometry has been applied to the Amaryllidaceae as well as many other alkaloid types.[15] This method offers several advantages over the conventional electron impact (E.I.) mass spectrometric determination: a quasi-molecular ion (QM^+) formed by protonation or hydride abstraction in ion–molecule collisions is always present; aliphatic hydroxy- and methoxy-functions can always be determined; and skeletal rearrangement is always absent.

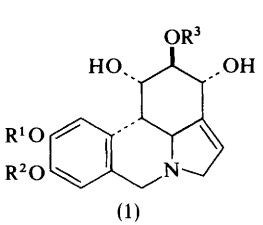
Interesting aspects of conformational analysis of these alkaloids have been concisely reviewed.[16]

The development of a quadrant rule for molecules possessing an asymmetric centre adjacent to an aromatic ring has led to assignment of absolute configuration for Amaryllidaceae as well as morphine and isoquinoline alkaloids.[17] Agreement with previous assignment on the basis of chemical evidence is observed for lycorine- and galanthamine-type systems. However, an opposite prediction is obtained for the 5,10*b*-ethanophenanthridine and the interrelated tazettine, criwelline, and montanine types.[17] These structures thus require re-examination. Exhaustive o.r.d. and c.d. studies of different structural types show that spectra may be used for rapid, reliable identification of new alkaloids.[18] Inter-system identification and intra-system identifications within a given structural type have been carried out.

Details have appeared of the earlier very interesting report which showed that tazettine (3; $R^1 = OMe$, $R^2 = H$) is an artifact produced from pretazettine (2; $R^1 = OMe$, $R^2 = H$) during isolation.[19] This type of rearrangement can be carried out with basic reagents also and applies with identical implications to the criwelline (3; $R^1 = H$, $R^2 = OMe$) –precriwelline (2; $R^1 = H$, $R^2 = OMe$) relationship. The interconversion of alkaloids possessing a 5,10*b*-ethanophenanthridine nucleus (4) with those of the aforementioned [2]benzopyrano[3,4-*c*]indole type (3) has been reported.[20] Carefully executed experiments show that variation in temperature, solvent, or pH is sufficient to alter the ring systems (3) and (4) and that the double bond at C-1 has no significant effect on the rearrangement. A well-known rearrangement of galanthamine (5; $R^1 = OH$,

[13] S. Tagaki and T. Katagi, *J. Pharm. Soc. Japan*, 1969, **89**, 1641.
[14] R. Razakov, V. N. Bochkarev, Kh. A. Abduazimov, N. S. Vul'fson, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 519; R. Razakov, V. N. Bochkarev, Kh. A. Abduazimov, N. S. Vul'fson, and S. Yu. Yunusov, *ibid.*, 1969, **5**, 280.
[15] H. M. Fales, H. A. Lloyd, and G. W. A. Milne, *J. Amer. Chem. Soc.*, 1970, **92**, 1590.
[16] G. A. Morrison, *Fortschr. Chem. org. Naturstoffe*, 1967, **25**, 299.
[17] G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, 1969, **25**, 5099.
[18] G. G. DeAngelis and W. C. Wildman, *Tetrahedron Letters*, 1969, 729.
[19] W. C. Wildman and D. T. Bailey, *J. Org. Chem.*, 1968, **33**, 3749; see also W. Doepke and P. W. Jeffs, *Tetrahedron Letters*, 1968, 1307.
[20] W. C. Wildman and D. T. Bailey, *J. Amer. Chem. Soc.*, 1969, **91**, 150.

R^2 = H) has been reinvestigated[21] and details of the transformation, (5) → narwedine (5; R^1 + R^2 = O) + (6), have been described.[22]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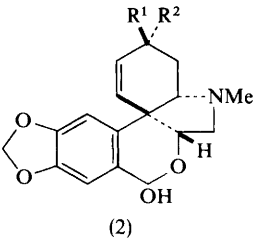
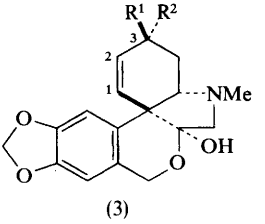
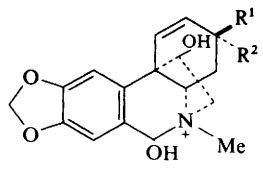

(2)


(3)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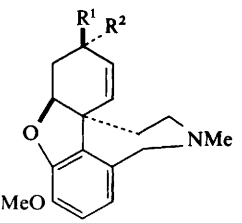
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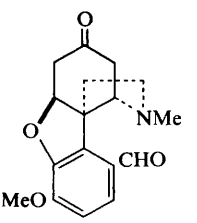
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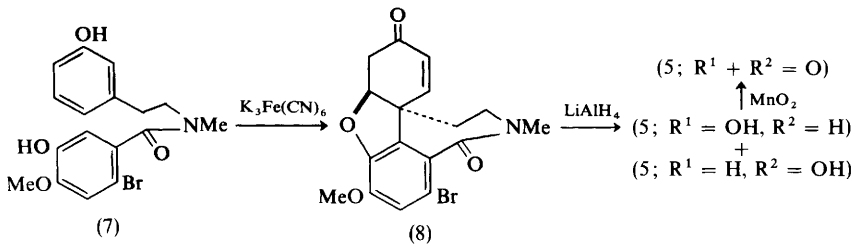
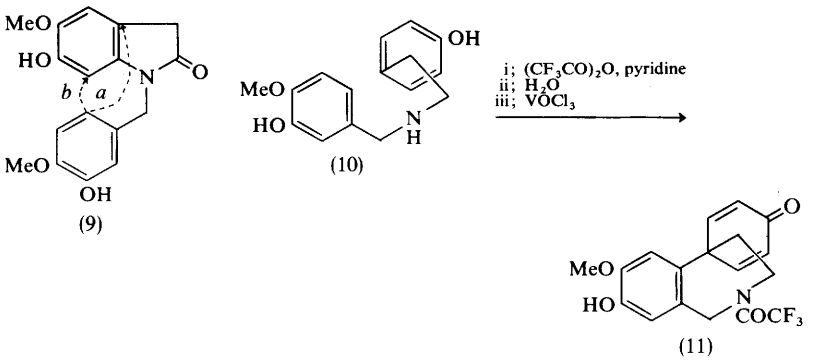

(7) (8)

An appreciation of the work which led to the successful synthesis of galanthamine *via* an oxidative coupling reaction[23] has aided Japanese workers in completing another total synthesis of this alkaloid.[24] When *para*-coupling is blocked by a bromine substituent and indole derivative formation is prevented by the presence of an amide function, as in (7), oxidation gives the required intermediate (8) in 40% yield. (±)-Galanthamine (5; R^1 = OH, R^2 = H) and (±)-epi-galanthamine (5; R^1 = H, R^2 = OH) are readily obtained from (8) and the former can be oxidised to (±)-narwedine. Similar thinking motivated the same group to subject the oxindole (9) to oxidative coupling conditions in the

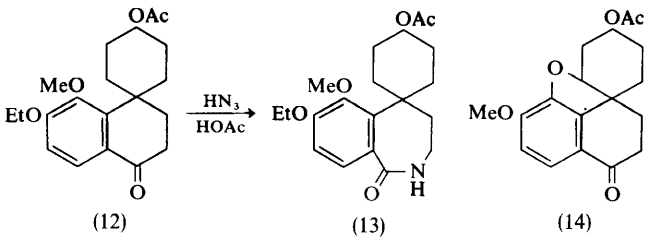
[21] A. Abdusamatov, Kh. A. Abduazimov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 194.
[22] J. G. Bhandarkar and G. W. Kirby, *J. Chem. Soc.* (*C*), 1970, 592.
[23] B. Franck and H. J. Lubs, *Annalen*, 1968, **720**, 131.
[24] T. Kametani, K. Yamaki, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1969, 2602.

hope of producing haemanthamine (bonding *a*) or lycorine (bonding *b*) alkaloids.[25] This, however, led to an undesired product whose structure has not been elucidated. A different oxidative coupling approach (10) → (11) has been used in the synthesis of a 5,10*b*-ethanophenanthridine type (4) alkaloid.[26] Upon deacetylation, intermediate (11) undergoes spontaneous Michael reaction (*N* to *C*) to yield the required skeleton.

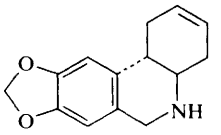


A totally different approach has been used in the synthesis of (±)-lycoramine[27] and some homologues of skeletal type (11).[28] Both schemes involve as the key stage a ring expansion of a spirotetralone to a benzazepine derivative [*e.g.*, (12) → (13)]. Slight modification of the initial steps leads to an improved preparation of the alkaloid through the Schmidt reaction on (14).[27]

Finally, several other attempts to synthesise lycorine [skeletal type (1)] have been recorded.[29] One of these uses ideas which were successfully executed earlier in the synthesis of related systems: the tricyclic intermediate (15) was prepared in three steps; however, it was not possible to attach the additional ring necessary for lycorine. Two other interesting intermediates, (16) and (19), which also failed



[25] T. Kametani, H. Yagi, K. Kawamura, and T. Kohno, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 645.
[26] M. A. Schwartz and R. A. Holton, *J. Amer. Chem. Soc.*, 1970, **92**, 1090.
[27] Y. Misaka, T. Mizutani, M. Sekido, and S. Uyeo, *J. Chem. Soc.* (*C*), 1968, 2954.
[28] T. Yashiro and H. Shirai, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 164.
[29] J. B. Hendrickson, R. W. Alder, D. R. Dalton, and D. G. Hey, *J. Org. Chem.*, 1969, **34**, 2667.



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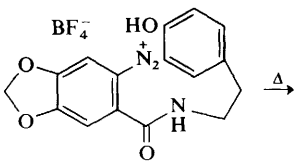
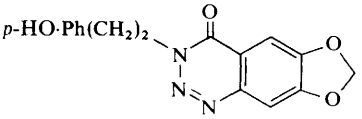


(16)



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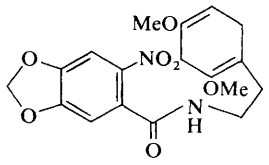

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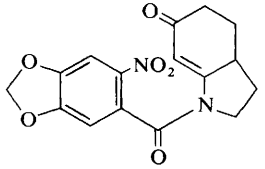

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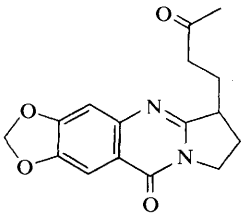


(20)

to give certain desired cyclisations, deserve mention: the diazonium salt (16) produced the benztriazinone (17), and the amide (19), prepared from (18), yielded the quinazolone derivative (20).

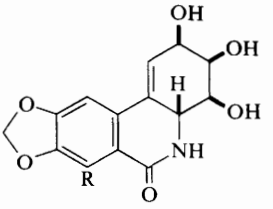
Narciclasine and narciprimine, two alkaloids of biosynthetic interest whose structures had been incorrectly assigned, are now shown to be (21; R = OH) and (22; R = OH) respectively.[30] The latter has been synthesised by a standard photochemical cyclisation route (23; $R^1 = R^2 = OCH_2Ph$) → (22; R^1 = OH). Arolycoricidine (22; R^1 = H), previously obtained[31] from lycoricidine (21; R^1 = H) was similarly prepared.[30]

The structure of the novel alkaloid miniatine (24) has been assigned with the aid of degradation, n.m.r., and c.d. studies.[32]

Cherylline (25) is a new example of a 4-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloid isolated from Amaryllidaceae plants. Description of its complete

[30] A. Mondon and K. Krohn, *Tetrahedron Letters*, 1970, 2123.
[31] T. Okamoto, Y. Torii, and Y. Isogai, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 1860.
[32] W. Döpke and M. Bienert, *Tetrahedron Letters*, 1970, 745.

characterisation[33] was rapidly followed by reports of absolute configuration assignment[34] and total synthesis.[35] Coincidentally, general syntheses of this structural type have appeared.[36]



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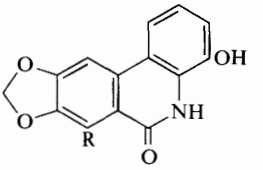

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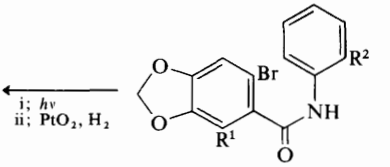

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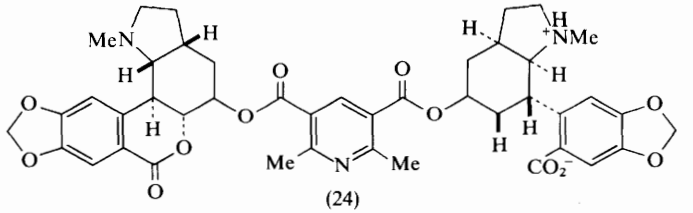

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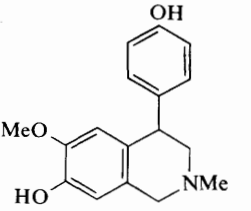
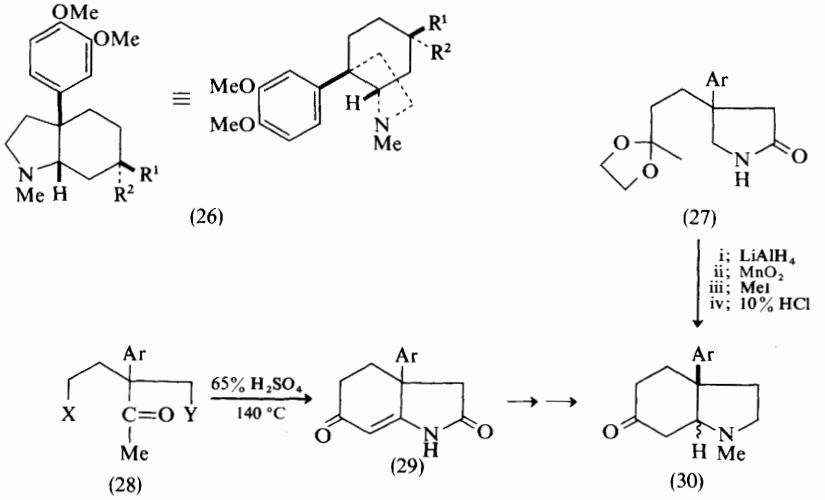


(25)

Recent indications point to the fact that the mesembrine alkaloids constitute a larger group than previously envisaged and for this reason it has been proposed that the mesembrane skeleton (26; $R^1 = R^2 = H$) be used as a basis for nomenclature of these alkaloids.[37] Combination of spectral (n.m.r. and c.d.) and chemical [saponification rates of (26; $R^1 = OAc$, $R^2 = H$) and acetylation rates of (26; $R^1 = OH$, $R^2 = H$) and the corresponding epimers] methods have been used to determine the absolute configuration of mesembrine (26; $R^1 + R^2 = O$).[37]

[33] A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Bailey, *J. Org. Chem.*, 1970, **35**, 1100.
[34] V. Toome, J. F. Blout, G. Grethe, and M. Uskokovic, *Tetrahedron Letters*, 1970, 49.
[35] A. Brossi and S. Teitel, *Tetrahedron Letters*, 1970, 417.
[36] J. M. Bobbitt and S. Shibuya, *J. Org. Chem.*, 1970, **35**, 1181.
[37] P. W. Jeffs, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1969, **91**, 3831.

The heavy synthetic activity in the mesembrine alkaloid field has been summarised.[38] Details and extensions of one of these efforts have appeared.[39] The key step involved a double cyclisation of (28; X = Y = CN; X = CN, Y = CO_2Me; X = CO_2Me, Y = CN) to give the intermediate (29) which was converted into (30) (*cis–trans* mixture) by unexceptional steps.[39a] Alternatively, the same compound (30; *cis*-form) can be prepared with less effort from the pyrrolidinone (27).[39b]



[38] R. H. F. Manske in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1970, vol. XII, p. 409; J. A. Joule, *Ann. Reports* (*B*), 1968, **65**, 507.

[39] [a] T. Ohishi and H. Kugita, *Tetrahedron Letters*, 1968, 5445; [b] H. Taguchi, T. Ohishi, and H. Kugita, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 1008.

12

Erythrina and Related Alkaloids

BY V. A. SNIECKUS

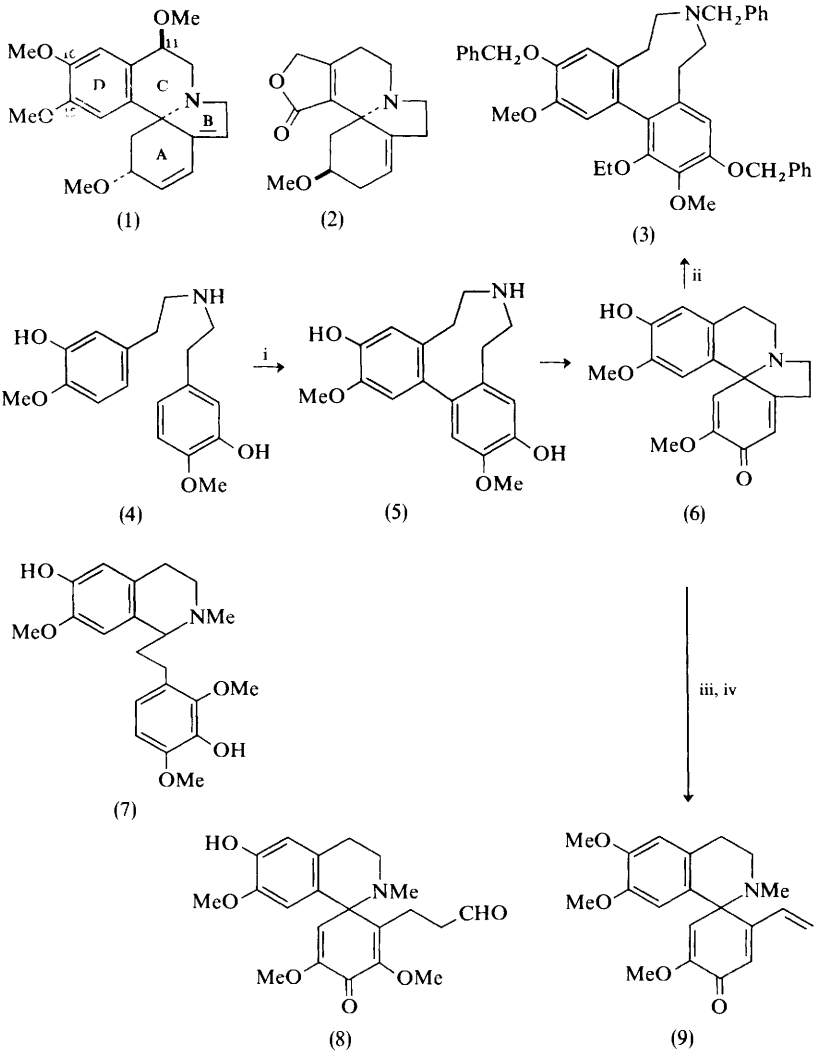
This section will discuss the Cephalotaxine [*e.g.*, (23)] and the Homoerythrina [*e.g.*, (19)] alkaloids as well as the normal *Erythrina* types.[1] The last two groups are clearly biogenetically related while the Cephalotaxine structure may be regarded as a rearranged *Erythrina* skeleton.

***Erythrina* Alkaloids.**—Although a small number of new alkaloids have been discovered, most of these show interesting structural features. Erysotrine has been obtained for the first time from a natural source (*Erythrina suberosa* Roxb.).[2] Erythroculine is the first case of an *Erythrina* alkaloid which bears a methoxycarbonyl-substituent at C-15.[3]

With the aid of decoupling experiments and the INDOR technique, it was possible to define completely the structure and stereochemistry of erythristemine (1) with the exception of the configuration at C-11.[4] In order to obtain the latter information, recourse was taken to *X*-ray analysis on the 2-bromo-4,6-dinitrophenolate salt of (1). This constitutes a new method and may be applicable elsewhere. Details of the structural and stereochemical elucidation of the interesting insecticidal alkaloid (2), which may be regarded as a ring-D degraded erythroidine structure, have appeared.[5]

Important synthetic thrusts in this area have been described.[6—9] The mechanism of the transformation (4) → (6) which proceeds in 35% yield [80% from (5)] has been shown to require both phenolic hydroxy-groups in (4) unblocked and therefore must involve *pp*-coupling and further oxidation to the intermediate (5).[6] The high yield may be due to the adoption of a favourable conformation and anion-radical exchange in the precursor of (5). An alternative indoline structure was eliminated from consideration as an intermediate since it

[1] R. K. Hill in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1967, vol. IX, p. 483; T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969, p. 167.
[2] H. Singh and A. S. Chawla, *Experientia*, 1969, **25**, 785.
[3] Y. Inubushi, H. Furukawa, M. Juichi, and M. Ito, *J. Pharm. Soc. Japan*, 1970, **90**, 2.
[4] D. H. R. Barton, P. N. Jenkins, R. Letcher, D. A. Widdowson, E. Hough, and D. Rogers, *Chem. Comm.*, 1970, 391.
[5] K. Wada, S. Marumo, and K. Munakata, *Agric. and Biol. Chem. (Japan)*, 1968, **32**, 1187.
[6] D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1208.

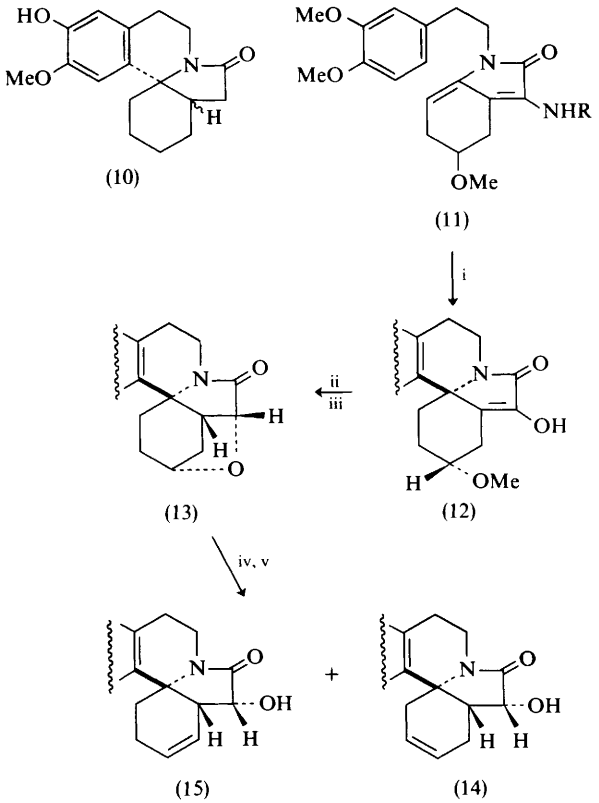


Reagents: i, $K_3Fe(CN)_6$; ii, $PhCH_2Cl$, K_2CO_3, EtOH; iii, NaH; iv, MeOTs, DMF.

failed to undergo the oxidative coupling reaction. Several interesting transformations are also reported, *e.g.*, (6 → 3) and (6 → 9). The oxidative coupling reaction has been tested on the 1-phenethyl-tetrahydroisoquinoline derivative (7).[7] Besides some fragmentation products, the aldehyde (8) and its $\alpha\beta$-unsaturated counterpart were isolated, indicating that undesired over-oxidation had

[7] T. Kametani, K. Fukumoto, M. Kawatzu, and M. Fujihara, *J. Chem. Soc.* (*C*), 1970, 922.

occurred. Neat one-step syntheses of the *Erythrina* skeleton have been developed.[8] For example, a *cis–trans* mixture of the erythrinanone (10) was obtained simply by refluxing a mixture of 3-hydroxy-4-methoxyphenethylamine and 2-ethoxycarbonylmethylcyclohexanone in ethanol under nitrogen.[8a] New



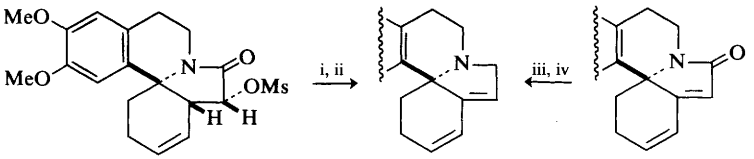
Reagents: i, H_3PO_4, MeOH, H_2O; ii, H_2–Ni, NaOH; iii, H_2SO_4; iv, Ac_2O, TsOH; v, H_2SO_4, MeOH.

applications of a somewhat similar cyclisation reaction (first reported in 1958) which yields A- and B-ring functionalised *Erythrina* compounds have been reported.[9] The series of steps (11) → (12) → (13) → (14) + (15) represents an

[8] [a] T. Kametani, H. Agui, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 1285; [b] T. Kametani, H. Agui, K. Saito, and K. Fukumoto, *J. Heterocyclic Chem.*, 1969, **6**, 453.

[9] [a] A. Mondon, K. F. Hansen, K. Boehme, H. P. Faro, H. J. Nestler, H. G. Vilhuber, and K. Boettcher, *Chem. Ber.*, 1970, **103**, 615; [b] A. Mondon, H. P. Faro, K. Boehme, K. F. Hansen, and P. R. Seidel, *ibid.*, 1970, **103**, 1286; [c] A. Mondon and P. R. Seidel, *ibid.*, 1970, **103**, 1298; [d] A. Mondon and K. Boettcher, *ibid.*, 1970, **103**, 1512; [e] A. Mondon and H. Witt, *ibid.*, 1970, **103**, 1522.

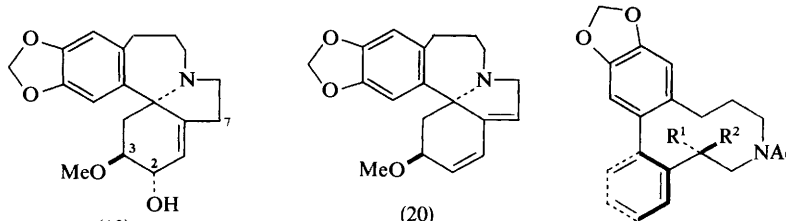
independent synthesis of compounds which form the basis of all earlier stereochemical assignments[1] of saturated *Erythrina* alkaloids.[9a] The mesylate ester (16) was used to prepare the doubly-unsaturated erythrinane (17) but the second step in this scheme was not reproducible.[9b] An alternative synthesis of (17) was therefore devised.[9b,9c] Hydride reduction of the thioamide corresponding to (18) gave a good yield of (17).



(16) (17) (18)

Reagents: i, $LiAlH_4$; ii, KOH; iii, P_2S_5; iv, Raney Ni, dioxan.

Homoerythrina Alkaloids.—The first representatives of this group, schelhammerine (19) and schelhammeridine (20), have been briefly reviewed.[10] Details concerning the structural elucidation[11] and crystal structure and absolute configuration[12] of these alkaloids have been reported. Schelhammeridine (20) undergoes[11b] an interesting acid-catalysed rearrangement to yield, after acetylation, the diastereomeric acetates (21; R^1 = OH, R^2 = H) and (21; R^1 = H, R^2 = OH) which are predicted from the absolute configuration of (20) to exhibit retention of diphenyl configuration but to have opposite C-7 configuration. On the other hand, schelhammeridine upon treatment with acetic anhydride yielded an *ON*-diacetyl derivative and this upon hydrolysis gave an *N*-acetate which is the optical antipode of (21; R^1 = H, R^2 = OH). It is elegantly shown that the latter is formed by inversion of biphenyl configuration of the initially

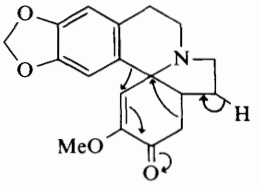


(19) (20) (21)

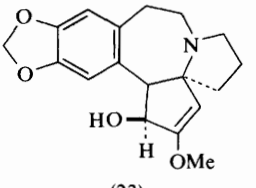
[10] R. W. Doskotch, *Ann. Reports Medicin. Chem.*, 1968, 322.

[11] [a] J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 2187; [b] S. R. Johns, J. A. Lamberton, A. A. Sioumis, and H. Suares, *ibid.*, 1969, **22**, 2203; [c] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *ibid.*, 1969, **22**, 2219.

[12] C. Kowala and J. Wunderlich, *Z. Kristallogr., Kristallgeometrie, Kristallphys. Kristallchem.*, 1969, **130**, 121.



(22)



(23)

formed *O*-acetyl derivative of (21; $R^1 = H$, $R^2 = OH$). Additional Homoerythrina alkaloids have been isolated from other Liliaceae plants.[13]

Cephalotaxine Alkaloids.—The structures of this group have been elucidated mainly by n.m.r. and mass spectroscopy[14,15] and confirmed by an *X*-ray crystallographic analysis.[16] This class of compounds, exemplified by cephalotaxine (23), bears an intriguing resemblance to the *Erythrina* alkaloids and may be derived by a dienol–phenol rearrangement, a bond migration, and reduction from the partially reduced form of a recognised precursor (22). The first step has ample *in vivo* and *in vitro* precedent in related alkaloid series.[17]

[13] N. Langlois, B. C. Das, and P. Potier, *Compt. rend.*, 1969, **269***C*, 639.
[14] R. G. Powell, D. Weisleder, C. R. Smith, jun., and I. A. Wolff, *Tetrahedron Letters*, 1969, 4081.
[15] R. G. Powell, D. Weisleder, C. R. Smith, jun., and W. K. Rohwedder, *Tetrahedron Letters*, 1970, 815.
[16] D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Letters*, 1969, 4085.
[17] H. R. Schütte in 'Biosynthese der Alkaloide,' ed. K. Mothes and H. R. Schütte, Deutscher Verlag der Wissenschaften, Berlin, 1969, pp. 387, 396, 407.

13
Indole Alkaloids

BY J. A. JOULE

This review covers the literature from the beginning of 1969 to the end of June 1970. Some work published earlier than this is included where background or subsidiary information is deemed necessary to the discussion; however, no older work that is already covered in the Manske 'Alkaloids' series is dealt with, although where appropriate, reference is made to the most recent relevant section of this series.

Within each sub-section, the material is dealt with in the order (*a*) physical measurements on known alkaloids or known systems, (*b*) new chemistry of known alkaloids or known systems, (*c*) new structures together with supporting chemical and physical evidence, (*d*) synthesis of model systems, and (*e*) synthesis of alkaloids.

1 Simple Indoles

Non-tryptamines.—The number of carbazole derivatives isolated from the Rutaceae is now fourteen. Besides the tricyclic compounds murrayanine[1a] (3-formyl-1-methoxycarbazole), glycozoline[1a] (3-methoxy-6-methylcarbazole), glycozolidine[1a] (2,4-dimethoxy-6-methylcarbazole), and (from *Clausena heptaphylla*) heptaphylline[2] (1), tetra- and penta-cyclic carbazoles have been obtained from *Murraya koenigii*.[3–7]

The next simplest compounds in the series are girinimbine[3] (2a) and murrayacine[3a,4] (2b). Catalytic reduction of the carbon–carbon double bond followed by lithium aluminium hydride reduction converted murrayacine into

[1] [a] R. H. F. Manske, 'The Alkaloids,' Academic Press, New York, 1968, Vol. X, chapter 10; [b] *ibid.*, chapter 5; [c] *ibid.*, Vol. XI, chapter 7; [d] *ibid.*, Vol. X, chapter 12; [e] *ibid.*, 1965, Vol. VIII, chapter 20; [f] *ibid.*, 1968, Vol. XI, chapter 2; [g] *ibid.*, Vol. XI, chapter 9.

[2] [a] B. S. Joshi, V. N. Kamat, A. K. Saksena, and T. R. Govindachari, *Tetrahedron Letters*, 1967, 4019; [b] B. S. Joshi and D. F. Rane, *Chem. and Ind.*, 1968, 685.

[3] [a] B. S. Joshi, V. N. Kamat, and D. H. Gawad, *Tetrahedron*, 1970, **26**, 1475; [b] N. L. Dutta and C. Quasim, *Indian J. Chem.*, 1969, **7**, 307.

[4] D. P. Chakraborty and K. C. Das, *Chem. Comm.*, 1968, 967.

[5] [a] N. S. Narasimhan, M. V. Paradkar, and V. P. Chitguppi, *Tetrahedron Letters*, 1968, 5501; [b] see also ref. 6.

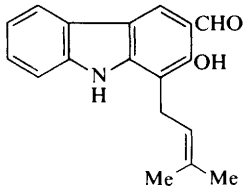
[6] S. P. Kureel, R. S. Kapil, and S. P. Popli, *Tetrahedron Letters*, 1969, 3857.

[7] D. P. Chakraborty, A. Islam, S. P. Busak, and R. Das, *Chem. and Ind.*, 1970, 593.

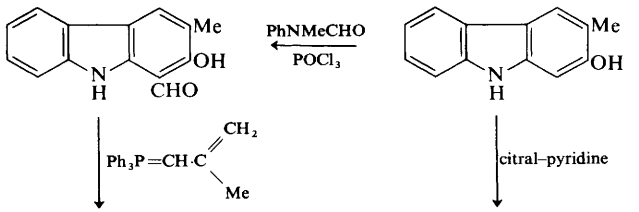
dihydrogirinimbine.[4] The relative positioning of the substituents, on only one of the aromatic rings, in the two related compounds and the position of the double bond in the oxygen ring were established[3a] by ozonolysis to 1-formyl-2-hydroxy-3-methylcarbazole, followed by decarbonylation to 2-hydroxy-3-methylcarbazole, which was synthesised.

Koenimbine[5b] and koenimbidine[5a] were assigned structures (2c) and (2d)[3a] on the basis of overall spectral comparability with (2a) and (2b), *i.e.* n.m.r. signals for one and two extra aromatic methoxy-groups respectively, and the aromatic proton signals (two singlets for koenimbine at τ 2.39 and 2.60 and three singlets for koenimbidine at τ 2.47, 2.60, and 3.10). Protons at carbazole 4- and 5-positions are easily recognised since they resonate at lower field than the rest of the aromatic hydrogen atoms.

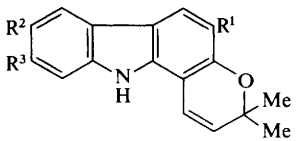
Mahanimbine (3a) on ozonolysis[3a,5] gave the same phenolic aldehyde as had girinimbine,[3a] establishing the common aromatic substitution pattern and D ring type. The remainder of the structure followed[5] from a highly characteristic[3,5] n.m.r. pattern for the alkenyl–methyl substituted chromene unit,

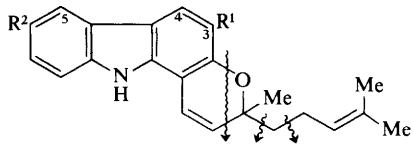


(1)



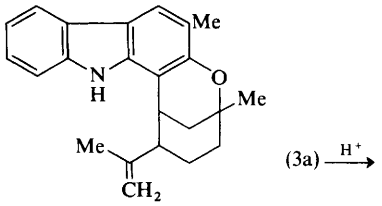
(2a) (3a)





(2)	R^1	R^2	R^3
a;	Me	H	H
b;	CHO	H	H
c;	Me	MeO	H
d;	Me	MeO	MeO

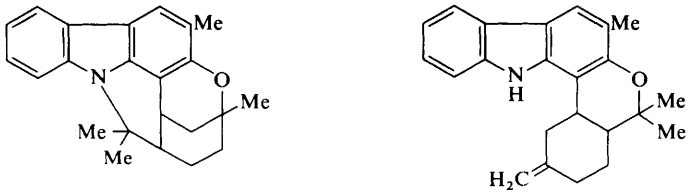
(3)	R^1	R^2
a;	Me	H
b;	H	Me



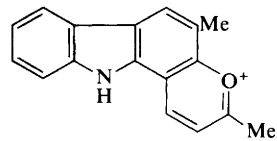
(4) (5)

in conjunction with important mass spectral fragmentation at the points indicated [arrows in (3)].

The positioning of the aromatic methyl group in isomahanimbine[3a] (3b) was made on the basis of the n.m.r. AB pattern for the carbazole 3- and 4-hydrogen atoms, at τ 3.3 and 2.3 respectively, and the broad singlet at τ 2.12 for the C(5)-hydrogen.



(6) (7)



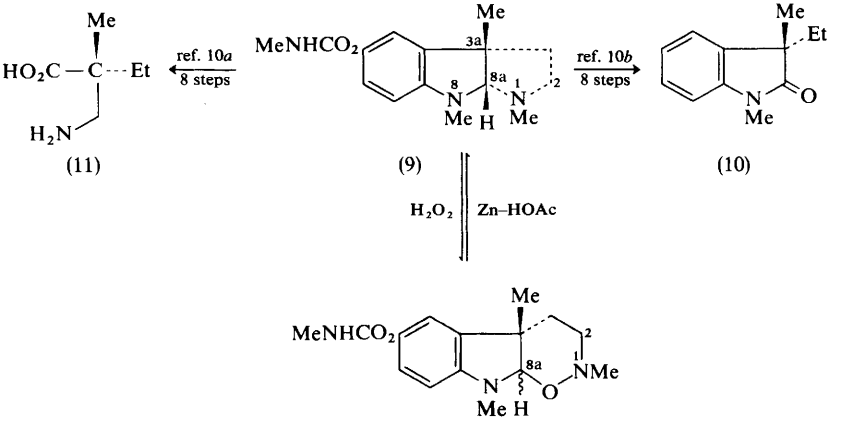
(8)

The structures for the remaining alkaloids in the group, cyclomahanimbine[6] (4), bicyclomahanimbine[6] (5), mahanimbidine[6] (6), and murrayazolidine[7] (7) are as yet less secure. Common to all of these compounds is a 2-oxycarbazole u.v. absorption, a carbazole 3-methyl group together with five remaining unsubstituted aromatic positions, and a significant mass spectral fragment ion at *m/e* 248 (8). Their n.m.r. spectra, as well as picking out the various methyl types, showed the presence of olefinic methylene groupings in cyclomahanimbine and murrayazolidine and the absence of *N*-hydrogen atoms in mahanimbidine. Since all four compounds are isomeric with (3a), with formulae of $C_{23}H_{25}NO$, the structures suggested for them at this stage rest heavily on the reasonable assumption that they contain, as with the simpler compounds in this group, a monoterpene unit apart from the 2-oxy-3-methylcarbazole nucleus. Indeed,

bicyclomahanimbine can be partially synthesised by acid treatment of mahanimbine and it is thought that, on account of this facile transformation, it may be an artifact. It will be noted that in the formulation (7) suggested for murrayazolidine the monoterpene unit is oriented differently from those in (4), (5), and (6).

Heptaphylline (1) has been synthesised[2b] by sequential C(3)-formylation and C(1)-isopentenylation of 2-hydroxycarbazole. 1-Formyl-2-hydroxy-3-methylcarbazole reacts with the Wittig reagent from 2-methylprop-1-en-3-yltriphenylphosphonium chloride–sodium hydroxide to generate girinimbine[8] (2a); 2-hydroxy-3-methylcarbazole[8,9] reacts with citral to give (±)-mahanimbine[9] (3a).

Non-isoprenoid Tryptamine Derivatives.—The relative and absolute configurations of (−)-physostigmine (9; 3a,*S* : 8a,*R*) have been thoroughly established[10] and since (−)-geneserine, (−)-*N*(8)-norphysostigmine, (−)-physovenine, and (−)-eseramine have all been correlated[1b] with this alkaloid by o.r.d. measurements, they also have the same absolute configuration. The *cis*-nature of the ring junction, assumed previously on the basis of reasonable chemical arguments, has now been confirmed[10a] utilising the nuclear Overhauser effect. It was shown that irradiation of the *C*(3a)-methyl group signal or the *N*(8)-methyl signal caused enhancement in the integrated intensity of the *C*(8a)-hydrogen signal. No comparable enhancement was noted when the *N*(1)-methyl signal was irradiated. It was concluded that the *C*(3a)-methyl and the *N*(8)-methyl groups are both *cis* to the *C*(8a)-hydrogen and that the aromatic nitrogen does not invert rapidly under the conditions of the measurement.



[8] N. S. Narasimhan, M. V. Paradkar, and A. M. Gokhale, *Tetrahedron Letters*, 1970, 1665.

[9] S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. Comm.*, 1969, 1120.

[10] [a] G. R. Newkome and N. S. Bhacca, *Chem. Comm.*, 1969, 385; [b] R. K. Hill and G. R. Newkome, *Tetrahedron*, 1969, **25**, 1249; [c] R. B. Longmore and B. Robinson, *Chem. and Ind.*, 1969, 622.

Two[10b,c] independent and different degradations have been carried out to establish the absolute stereochemistry, and in each case the final compound contained only the *C*(3a) asymmetric centre. One approach[10b] was to degrade the alkaloid to the oxindole (10), the enantiomorph of which was then synthesised starting from (*R*)-(−)-2-methyl-2-phenylbutyric acid. In the second approach[10c] the molecule was broken down to an amino-acid (11) which was characterised as its 2,4-dinitrophenyl derivative. Its enantiomer was synthesised from 3-ethyl-3-methoxycarbonyl-3-methylpropionic acid of known absolute configuration.

Geneserine, previously considered to be the *N*(1)-oxide of physostigmine on the very reasonable basis that it is produced when the latter is treated with hydrogen peroxide and can be reduced back to physostigmine with zinc–acid, is now considered[11] to have the structure (12). In addition to the absence of $M - 16$, $M - 17$, and $M - 18$ mass spectral fragment peaks usually associated with *N*-oxides, the changes in n.m.r. chemical shifts in going from physostigmine to geneserine are inconsistent with an *N*-oxide formulation. Principal in the argument is the change in the resonance position of the *C*(8a)-hydrogen, which is the *only* signal to move significantly, by 38 Hz downfield. If geneserine were an *N*-oxide, the chemical shifts of both *N*(1)-methyl and *C*(2)-hydrogens would have been expected to differ significantly, on the basis of analogy with the spectral differences between *N*-methylpyrrolidine and its *N*-oxide. The *N*-oxide is now presumed to be an intermediate in the peroxidic treatment of physostigmine; ring-opening and recyclisation then give geneserine.

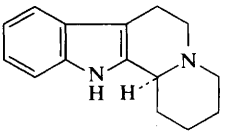
As well as known 5-oxytryptamine types, *Virola* species,[12] used in the preparation of intoxicating snuffs, contain 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline and 6-methoxy-1,2-dimethyl-1,2,3,4-tetrahydro-β-carboline. An isomer of this last alkaloid, 6-methoxy-2,9-dimethyl-1,2,3,4-tetrahydro-β-carboline, has been isolated[13] from *Phalaris arundinacea.*

A variety of β-carboline and tetrahydro-β-carboline compounds have come to light recently which contain either a fourth ring, or four rings and a second nitrogen, or in some cases five rings and a second nitrogen; these are clearly not related to the main body of monoterpene-tryptamine alkaloids.

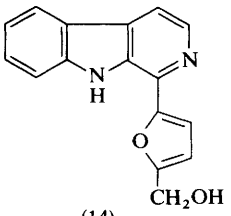
The simplest of the group is the base (13), isolated[14] from *Dracontomelum mangiferum* and was shown to be in partially racemic form by the synthesis and resolution of the compound.[15] The (−)-isomer (13) slightly predominates in the natural mixture; the absolute configuration was assigned by o.r.d. comparison[15,16a] with yohimbine and ψ-yohimbine. In fact this is the only simple tetrahydro-β-carboline alkaloid yet obtained which is not completely racemic.

[11] C. Hootelé, *Tetrahedron Letters*, 1969, 2713.
[12] S. Agurell, B. Holmstedt, J.-E. Lindgren, and R. E. Schultes, *Acta Chem. Scand.*, 1969, **23**, 903.
[13] R. C. S. Audette, H. M. Vigayanagar, J. Bolen, and K. W. Clark, *Canad. J. Chem.*, 1970, **48**, 149.
[14] S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Austral. J. Chem.*, 1966, **19**, 1951.
[15] S. Yamada and T. Kunieda, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 499; J. Pospíšek, Z. Koblicová, and J. Trojánek, *Chem. and Ind.*, 1969, 25.
[16] [a] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 801; [b] J. Harley-Mason and C. G. Taylor, *Chem. Comm.*, 1969, 281.

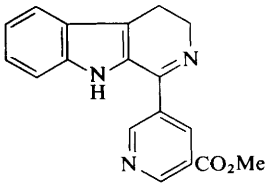
Perlolyrine[17] (14) is an alkaloid from the perennial rye grass *Lolium perenne*, and is of a different type from the alkaloids obtained previously from *Lolium* species. The alkaloid has been synthesised by a standard Pictet–Spengler synthesis using 5-acetoxymethyl-2-formylfuran and tryptophan, followed by oxidative dehydrogenation–decarboxylation.



(13)



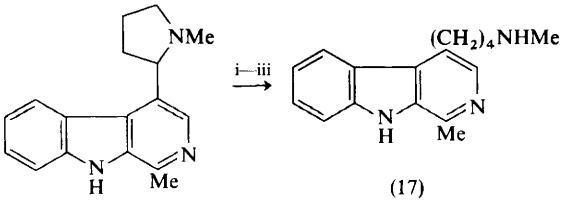
(14)



(15)

The bark of the Nigerian species *Nauclea diderrichii*[18] contains C_8-pyridine alkaloids, harman types, and three similar bases, one of which has been synthesised by a standard route and thereby proved to have the structure (15).

Brevicolline[19a] (16) and brevicarine[19b] (17) from *Carex brevicollis* have been interrelated[19c] as shown. Their structures rest on spectral measurements and



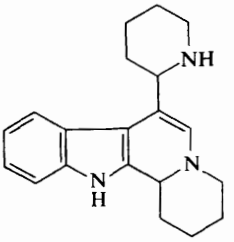
(16) (17)

Reagents: i, PhCOCl; ii, H_2–Pt; iii, KOH

[17] J. A. D. Jeffreys, *J. Chem. Soc.* (*C*), 1970, 1091.

[18] S. McLean and D. G. Murray, *Canad. J. Chem.*, 1970, **48**, 867.

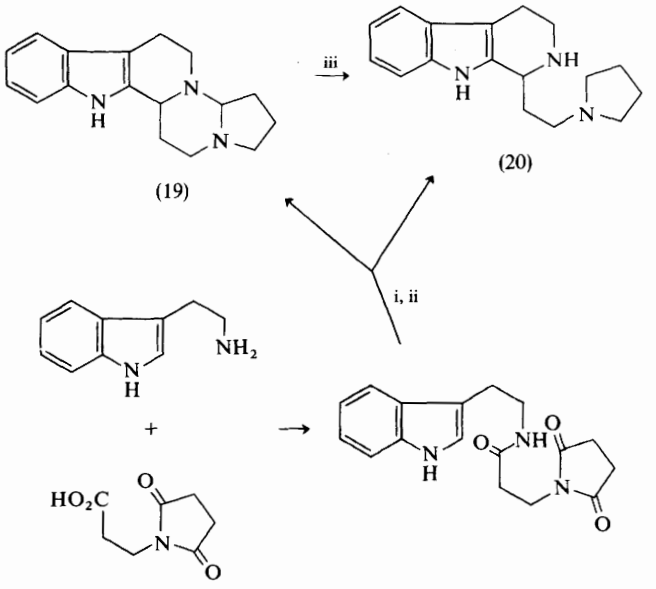
[19] [a] P. A. Vember, I. V. Terent'eva, and A. V. Ul'yanova, *Khim. prirod. Soedinenii*, 1968, **4**, 98 (*Chem. Abs.*, 1968, **69**, 77569*z*); [b] I. V. Terent'eva, G. V. Lazur'evskii, and T. I. Shirshova, *Khim. prirod. Soedinenii*, 1969, **5**, 397 (*Chem. Abs.*, 1970, **72**, 67166*p*); [c] P. A. Vember and I. V. Terent'eva, *Khim. prirod. Soedinenii*, 1969, **5**, 404 (*Chem. Abs.*, 1970, **72**, 100967*a*).



(18)

on the oxidation[19a] of brevicolline to 4-carboxy-1-methyl-β-carboline, the methyl ester of which was synthesised.

Two pentacyclic bases containing tryptamine units and a second nitrogen have been reported. The structure (18) for nitrarine, an optically inactive base from *Nitraria schoberi*, relies at the moment on spectral measurements.[20] Elaeocarpidine, an optically inactive alkaloid which co-occurs with indolizidine alkaloids in *Elaeocarpus densiflorus*, has been examined fully and proved to have the structure (19). Central to the structure determination was a hydrogenolysis, in acid solution, of the N–C–N system to give dihydroelaeocarpidine



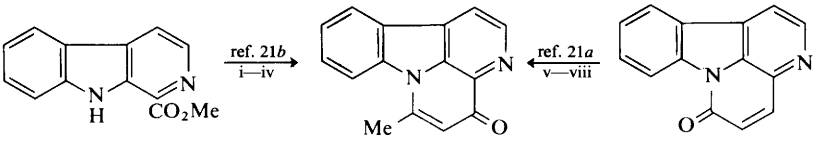
Scheme 1

Reagents: i, $POCl_3$; ii, $LiAlH_4$; iii, Zn–HCl.

[20] M. Normatov and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 139 (*Chem. Abs.*, 1968, **69**, 77570*t*).

(20) which, after reaction with methyl iodide, gave *N*-methylpyrrolidine on Hofmann degradation. This, in conjunction with the isolation in reasonably good yield of 1-ethyl-β-carboline by selenium dehydrogenation of the alkaloid, and compatible spectral measurements, made the structure (19) certain.[16a] The synthesis[16b] of the base has been achieved (Scheme 1), the final step giving a mixture of (19) and (20).

Norisotuboflavine (21) has been synthesised[21] from canthinone[21a] (22) and from 1-methoxycarbonyl-β-carboline[21b] (23) (Scheme 2).



(23) (21) (22)

Scheme 2

Reagents: i, MeCH:CH·CO_2Me–NaH; ii, H^+; iii, $Me_3PhN^+Br_3^-$; iv, LiCl; v, H_2–Pd/C; vi, MeMgI; vii, MeOH–HCl; viii, SeO_2.

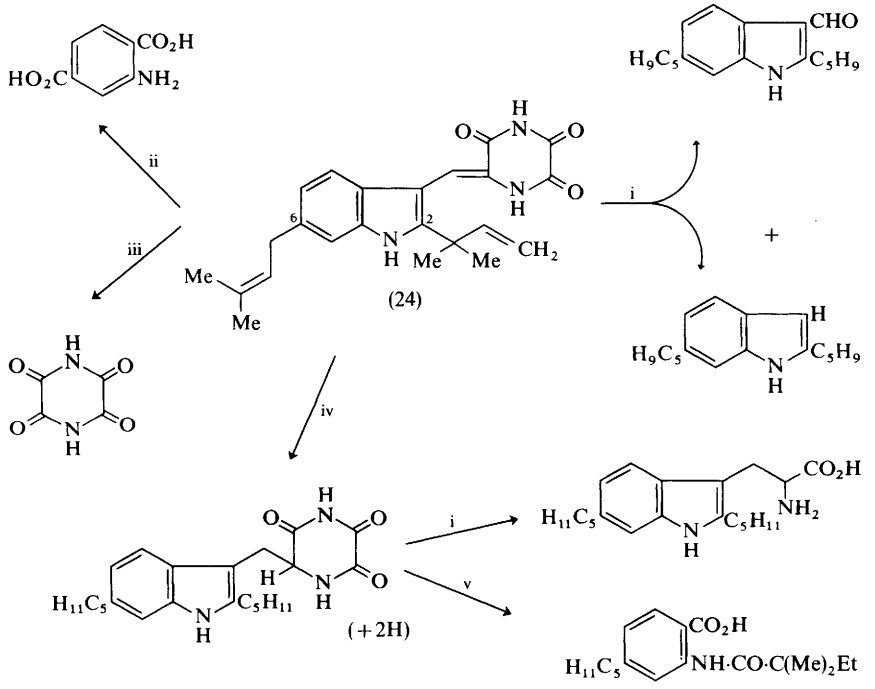
2 Isoprenoid-tryptamine and -tryptophan Alkaloids

Non-terpenoid Bases.—A number of intriguing indole and tryptophan derivatives carrying one or more unlinked isoprene units have appeared recently. For example, 1-isobutyl-1,2,3,4-tetrahydro-β-carboline has been obtained from *Eleagnus commutata*[22] and 4-isopentenyltryptophan, previously known as a good biological precursor of the ergot alkaloids, has been isolated from an ergot strain which had been fed with ethionine as antagonist.[23a] 6- and 7-Isopentenylindoles have been isolated[24] from a liverwort, *Riccardia sinuata*.

Neoechinuline,[25] $C_{23}H_{25}N_3O_3$ (24), isolated from *Aspergillus amstelodami*, the organism which produces echinulin, is made up of two isoprene units, one at the unusual (see also above) indole 6-position, a tryptophan residue, and an oxalic acid unit. In a classically thorough structure determination (Scheme 3), the indolic compound was oxidised to 2-aminoterephthalic acid, establishing the original 6-alkenyl-substitution. Catalytic reduction gave hydroneoechinulin, $C_{23}H_{33}N_3O_3$, in which the three carbon–carbon double bonds and one (as yet unidentified) carbon–oxygen double bond had been reduced. Oxidation of hydroneoechinulin gave rise to an *N*-acyl-4-isopentylanthranilate. Hydrolysis of the amide link of this and the isolation of 2,2-dimethylbutyric acid showed

[21] [a] H. J. Rosenkranz and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 565; [b] F. J. McEvoy and G. R. Allen, *J. Org. Chem.*, 1969, **34**, 4199.
[22] G. W. A. Slywka and R. A. Locock, *Tetrahedron Letters*, 1969, 4635.
[23] [a] S. Agurell and J.-E. Lindgren, *Tetrahedron Letters*, 1968, 5127; [b] J. E. Robbers and H. G. Floss, *Tetrahedron Letters*, 1969, 1857.
[24] V. Benešová, Z. Samek, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1969, **33**, 1807.
[25] M. Barbetta, G. Casnati, A. Pochini, and A. Selva, *Tetrahedron Letters*, 1969, 4457.

that the second isoprene unit was originally attached at the indole 2-position, and confirmed the n.m.r. spectral indications that it was linked *via* the *gem*-dimethyl substituted carbon. Alkaline hydrolysis of hydroneoechinulin gave 2,6-di-isopentyltryptophan, whereas base cleavage of the original compound gave a mixture of 3-formyl- and 3-unsubstituted-2,6-dialkenylindoles. Ozonolysis of neoechinulin to tetraketopiperazine completed the proof of overall structure.[25] The stereochemistry of the double bond of the dehydrotryptophan residue is not yet known.



Scheme 3

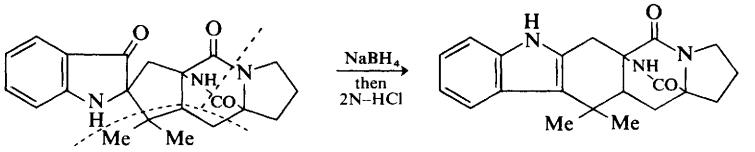
Reagents: i, KOH; ii, $KMnO_4$–OH^-; iii, O_3; iv, H_2–Pt; v, $MeCO_3H$ then Zn.

Penicillium brevi-compactum has yielded a group of neutral compounds which have been called the brevianamides. Brevianamides A and E have been examined[26] in detail, and assigned structures on the bases of spectral measurements, some simple transformations and, most importantly, an intuitive combination of these data with the experimentally proven biogenetic precursor units.

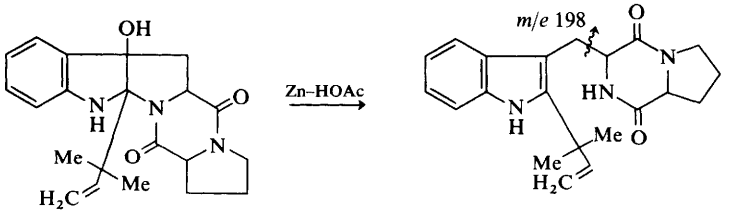
Brevianamide A (25), $C_{21}H_{23}N_3O_3$, had an indoxyl u.v. absorption and was converted by sequential borohydride and acid treatments into a 2,3-disubstituted

[26] A. J. Birch and J. J. Wright, *Tetrahedron*, 1970, **26**, 2329.

indole (26), in a type of rearrangement previously well known for simpler 2,2-disubstituted indoxyls. I.r. evidence suggested the presence of a diketopiperazine unit, which was shown to carry only one exchangeable *N*-hydrogen. It was further shown that in this unit both positions α to the carbonyl groups carried no hydrogen, since no exchange could be effected under appropriate basic conditions. N.m.r. and hydrogenation evidence showed that the molecule contained only the unsaturation associated with the indoxyl nucleus and hence is hexacyclic. Also clear from the n.m.r. spectrum was the presence of two methyl groups attached to quaternary, saturated carbon.



(25) (26)



(27) (28)

All this evidence could be rationalised when it was established that just three biogenetic precursor units, tryptophan, proline, and a mevalonate-derived isoprene unit were involved and could account for all of the carbon atoms of the molecule. Neither acid nor alkaline hydrolysis led to the removal of an amino-acid unit, showing each to be joined to the rest of the molecule by more than simple amide linkages. A combination of the chemical, spectral, and biosynthetic evidence and the assumption that the tryptophan side chain had migrated to the indole α-position during biogenesis, led to the formula (25) as the most likely for this intriguing compound; the biogenetic precursor units are indicated by the dotted lines in (25). An alternative structure with the isoprene unit linked to the indole the other way round is considered less likely, partly because in the borohydride–acid rearrangement similarly substituted *C*(2)-substituents would be expected to have comparable migratory aptitudes and to lead to a mixture of products; only one compound, considered to be (26) by migration of the quaternary centre, was obtained.

Brevianamide E, $C_{21}H_{25}N_3O_3$ (27), a dihydroindolic compound (u.v. spectrum), had i.r. absorption compatible with the presence of a diketopiperazine unit. The n.m.r. spectrum indicated the presence of an isoprene unit, linked *via*

the *gem*-dimethyl-substituted carbon, but in this case retaining unsaturation in the form of a vinyl group.

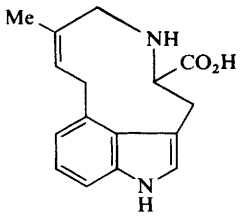
In contrast with brevianamide A, brevianamide E gave one mole of proline cleanly on acid hydrolysis. Zinc–acetic acid reduction produced a degradation product (28), characterised as an indole; an important mass spectral fragment ion at *m/e* 198 corresponds to cleavage as shown.

Since the original compound is an indoline and contains a hydroxy-group, the structure (27) is suggested in the light of the reduction to a hydroxy-group-free indole. It is interesting to note that the indolinic u.v. absorption of brevianamide E is unaffected by acid. Though it contains a *gem*-diamino-group,[27] the aliphatic nitrogen is part of an amide group and thus is not easily protonated. The proximity of the amide group is apparently sufficient to deter protonation at the aromatic nitrogen.

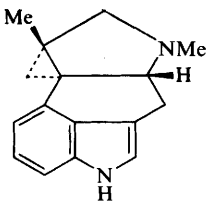
Several monoterpene-indole alkaloids are known in which 3-hydroxylation of the indole system has been followed by cyclisation on to the α-position [*e.g.*, (64)].

It has been shown[28] that anion-exchange resins can sometimes be useful for the epimerisation at C(8) of isolysergic acid amides to give compounds in the more useful lysergic acid series.

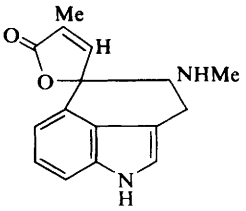
Clavicipitic acid (29) is another compound from an interrupted biogenesis which was obtained[23b] from a *Claviceps* species by feeding ethionine as antagonist. The structure follows more or less from the obvious spectral measurements and from feeding experiments which showed that mevalonate and tryptophan, in which the hydrogen α to carbonyl was retained, were both incorporated.



(29)



(30)



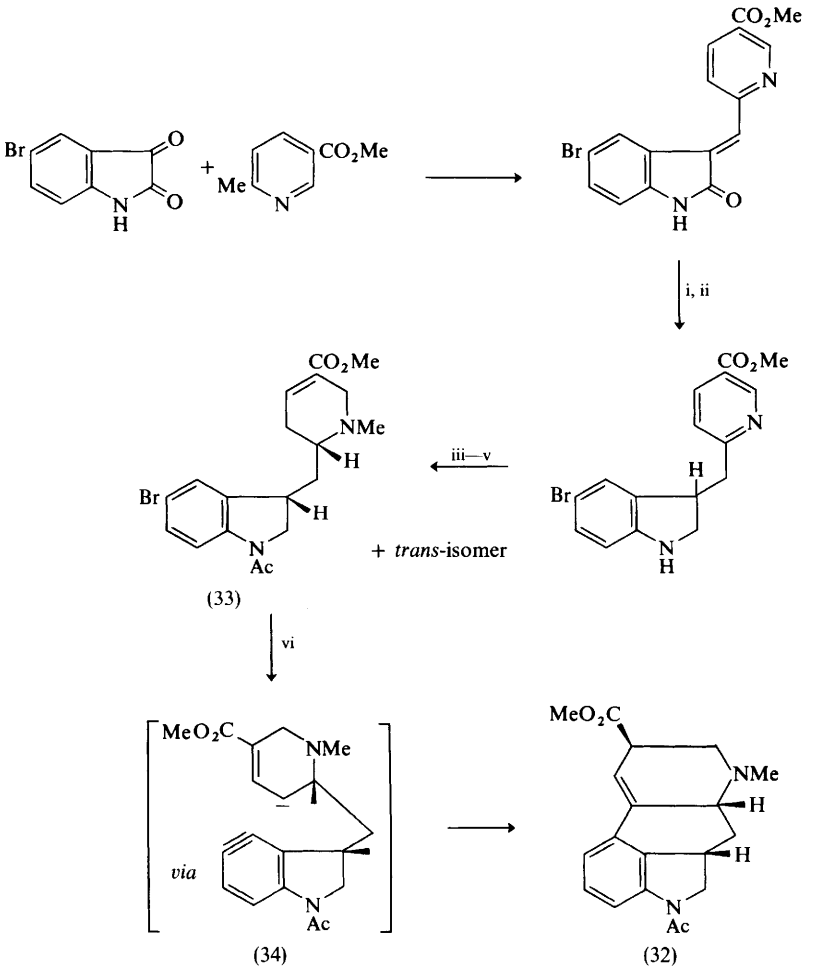
(31)

Cycloclavine (30), from *Ipomoea hildebrandtii*, contains a cyclopropane ring, as established by an *X*-ray analysis of its methobromide salt.[29] The rugulovasines A and B (31) are optical isomers from *Penicillium concavo-rugulosum*.[30] Their structures are supported by an analysis of their n.m.r. spectra and by the co-occurrence of chanoclavine in the same culture.

[27] B. Robinson, *Chem. and Ind.*, 1963, 218.
[28] A. Černý and M. Semonský, *Coll. Czech. Chem. Comm.*, 1969, **33**, 694.
[29] D. Stauffacher, P. Niklaus, H. Tscherter, H. P. Weber, and A. Hofmann, *Tetrahedron*, 1969, **25**, 5879.
[30] S. Yamatodani, A. Yutaka, A. Matsukura, S. Ohmomo, and M. Abe, *Agric. and Biol. Chem. (Japan)*, 1970, **34**, 485.

An elegant synthesis[31] (Scheme 4) of (±)-methyl *N*-acetyldihydrolysergate (32) makes critical use of an intramolecular addition of an enolate anion to a benzyne, both being generated *in situ* [step (33) → (32), *via* (34)].

Syntheses[32] of ergocristine, α- and β-ergokryptine, and ergocornine, by reaction of the appropriate synthetic polypeptide fragment with *d*-lysergic acid,



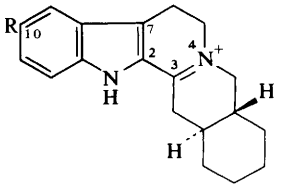
Scheme 4

Reagents: i, Zn–AcOH; ii, B_2H_6; iii, Ac_2O; iv, MeI; v, $NaBH_4$; vi, $NaNH_2$–NH_3(liq).

[31] M. Julia, F. Le Goffic, J. Igolen, and M. Baillarge, *Tetrahedron Letters*, 1969, 1569.
[32] P. A. Stadler, S. Guttmann, H. Hauth, R. L. Huguenin, E. Sandrin, G. Wersin, H. Willems, and A. Hofmann, *Helv. Chim. Acta*, 1969, **52**, 1549.

have served to clear up some stereochemical uncertainties in the peptide portions of these alkaloids.

Monoterpene Bases.—*Yohimbine–Corynantheine (and Related Oxindoles)–Picraline Group.* It is well known that 3,4-dehydroyohimbane (35a) is reduced by zinc–acetic acid to a mixture of yohimbane (35c) and ψ-yohimbane (35d); however, when 10-methoxy-3,4-dehydroyohimbane (35b) was similarly treated,[33] a 2,3,4,7-tetrahydro-derivative (17% yield) was formed as well as the corresponding 10-methoxy-yohimbanes. It was shown that this did not arise by further reduction of either of the methoxy-yohimbanes and no explanation is yet available for this interesting difference. Reserpine, a 6-methoxyindole, underwent C(3)–N(4) bond fission on reaction with zinc–acetic acid, as did indoles with no ring A methoxy-group.[34] Cleavage of the C(3)–N(4) bond with the formation of *N*(4)-cyano-*C*(3)-alkoxy- or hydroxy-seco-derivatives was observed when yohimbine, ψ-yohimbine, and methyl reserpate were subjected to von Braun degradation conditions in alcohol or aqueous solution.[35]

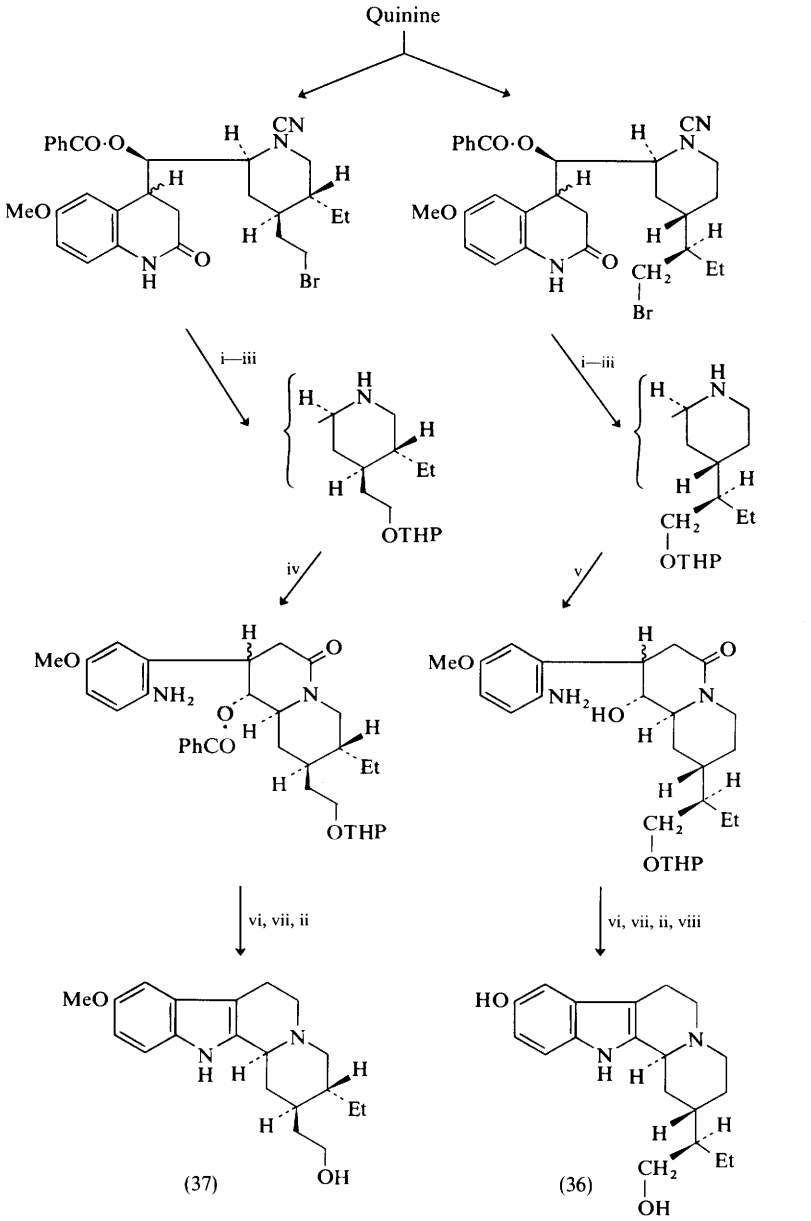


(35) R
a; H
b; MeO
c; H, 3,4-dihydro,3-α-H
d; H, 3,4-dihydro,3-β-H

Following earlier work, quinine has now been transformed into dihydrohunterburnine α- and β-methochlorides,[36a] dihydroantirhine,[36a] 10-methoxydihydrocorynantheol,[36b] and ochrosandwine.[36b] Scheme 5 depicts the formation of dihydrohunterburnine (36) and 10-methoxydihydrocorynantheol (37). These transformations establish the absolute configurations of the hunterburnine metho-salts, and of 10-methoxydihydrocorynantheol and ochrosandwine, and confirm that of antirhine.

Veneserpine from *Alstonia venenata* is identical with reserpine except that the trimethoxybenzoyl unit is replaced by a 3,4-methylenedioxy-5-methoxybenzoyl group.[37] An n.m.r. study has elucidated the full relative stereochemistry of tetraphyllinine (38)[38] from *Rauwolfia discolor.*

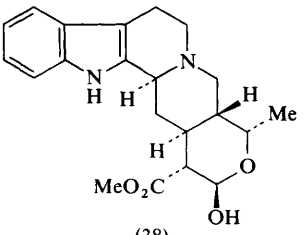
[33] G. C. Morrison, W. A. Cetenko, and J. Shavel, *J. Heterocyclic Chem.*, 1969, **6**, 577.
[34] A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1968, **24**, 5115.
[35] J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 1969, **91**, 4317.
[36] [a] Y. K. Sawa and H. Matsumura, *Tetrahedron*, 1969, **25**, 5319; [b] *ibid.*, p. 5329.
[37] A. Chatterjee, P. L. Majumder, and B. C. Das, *Chem. and Ind.*, 1969, 1388.
[38] L. Fonzes, C. Lucas, A. Pavia, and F. Winternitz, *Phytochemistry*, 1969, **8**, 1797.



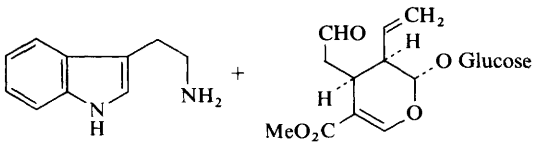
Scheme 5

Reagents: i, AgOAc–pyridine; ii, H_2O–H^+; iii, TsOH–dihydropyran; iv, Me_2CO–heat; v, aq. MeOH–heat, then MeCN–heat; vi, $LiAlH_4$; vii, Bu^{t}OLi–Ph_2CO; viii, BBr_3.

The isolation and characterisation of vincoside[39a] (39a), isovincoside[39a] (39b), and *N*(4)-acetylvincoside[39a] from *Vinca rosea*, and of strictosidine[39b] [same overall structure as (39) but not yet stereochemically defined] from *Rhazya stricta*, have certainly provided the most exciting and significant new structures in this



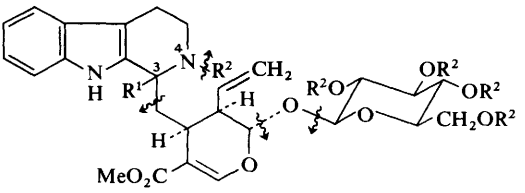
(38)



(40)

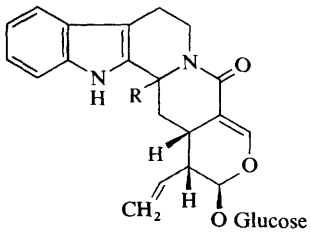
pH 4.5
37 °C

(39a) + (39b)



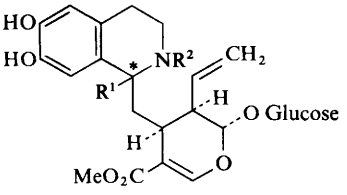
(39) R^1 R^2
a; α-H H
b; β-H H
c; α-H Ac

aq Na_2CO_3–R.T., (39a) → (42a)
aq Na_2CO_3–70 °C, (39b) → (42b)



(42) R
a; α-H
b; β-H

[39] [a] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1193; [b] G. N. Smith, *Chem. Comm.*, 1968, 912; [c] A. R. Battersby, A. R. Burnett, E. S. Hall, and P. G. Parsons, *Chem. Comm.*, 1968, 1582.



(41) R^1 R^2
a; α-H H
b; β-H H
c; α-H Ac

group of alkaloids in the recent literature. Vincoside (39a) has been shown[39c] to play a vital intermediary role in the biogenesis of all three monoterpene indole alkaloid types.

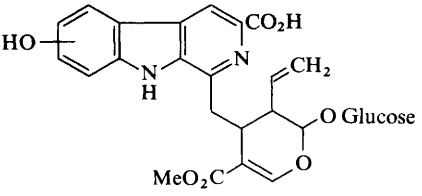
Vincoside[39a] differs from isovincoside (39b) only in the stereochemistry at C(3). The mass spectral fragmentation [arrows in (39)] of penta-acetylvincoside (39c) was highly characteristic and helpful in structure proof.[39a,b] U.v. and n.m.r. spectra confirmed the presence of unconjugated indole and O·C : C·CO_2Me chromophores in the molecule. This information, taken with the partial synthesis of a mixture of vincoside (major) and isovincoside (minor) from tryptamine and secologanin (40) of known structure and absolute configuration, was enough to establish[39a] both structure and absolute stereochemistry for vincoside and isovincoside, with the exception of the stereochemistry at C(3). This was arrived at by a comparison[39a] of the molecular rotation differences resulting from *N*-acetylation in the vincoside and isovincoside series with the corresponding differences for the epimeric tetrahydroisoquinolines (41a) and (41b). The absolute configuration at the starred centre of (41c) has been rigorously established[39a] by chemical correlation with the primary standards.

Vincoside is converted by mild base (conditions which do not affect isovincoside) into a lactam[39a] (42a). Isovincoside gave a corresponding compound (42b) on more vigorous basic treatment. This difference in reactivity can be rationalised in terms of the assigned *C*(3)-stereochemistry for the two precursors, since models indicate that fewer non-bonded interactions exist in the lactam (42a), and by implication in the transition state leading to it, than in the isomeric lactam[39a] (42b).

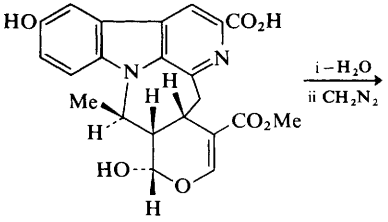
Adina cordifolia has yielded a pair of β-carboline acids, cordifoline[40a] (43) and adifoline[40b] (44), which are closely related to the vincosides in structural type. In both compounds the carboxy-group of precursor tryptophan is retained; very few monoterpene indole alkaloids have been obtained which do still retain this feature, though of course, classical methods of alkaloid isolation would automatically lose such compounds in discarded acidic fractions.

The structure of adifoline was established by n.m.r. and mass spectroscopy.[40b] Both dimethyldehydroadifoline (45), easily obtained from the alkaloid, and

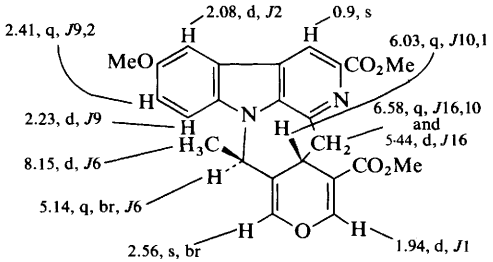
[40] [a] R. T. Brown and L. R. Row, *Chem. Comm.*, 1967, 453; [b] R. T. Brown, K. V. J. Rao, P. V. S. Rao, and L. R. Row, *Chem. Comm.*, 1968, 350.



(43)



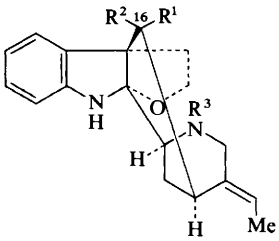
(44)



(45)

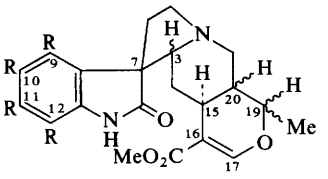
adifoline itself had well defined and helpful n.m.r. spectra, as can be seen for example from the values given for the degradation product (45).

Lonicerine, from *Callichilia barteri*, has been shown to be 16-epi-aspidodasycarpine[41] (46a). The methoxy-signal in the n.m.r. spectrum of lonicerine was at τ 7.02, compared with that (τ 6.28) for the isomeric aspidodasycarpine (46b) which was at the normal position. The high-field signal in the present instance is accounted for by the proximity of the ester function to the aromatic ring. The *N*(4)-acetyl derivatives of both alkaloids were converted by base into the same desformyl degradation product (46c), which confirmed the structure and absolute stereochemistry of lonicerine.

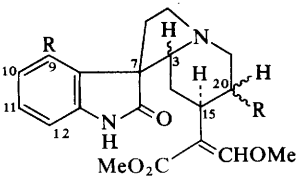


(46)	R^1	R^2	R^3
a;	CH_2OH	CO_2Me	H
b;	CO_2Me	CH_2OH	H
c;	CO_2Me	H	Ac

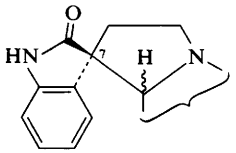
[41] J. Naranjo, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1970, **53**, 749.



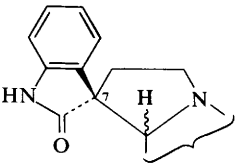
(47)



(48)

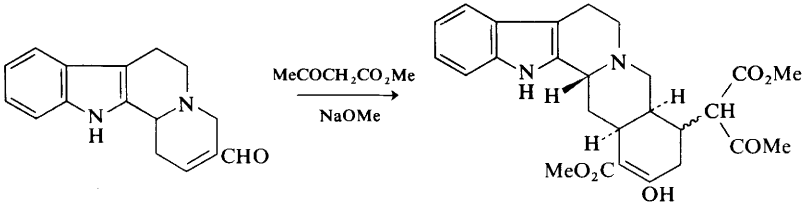


(49)



(50)

Much of the stereochemistry of the heteroyohimbine (47) and corynantheine (48) oxindole alkaloids has now been elucidated and general methods[42a—e] for doing this have been discussed. Given below are two tables which summarise the present position for each type, *i.e.* the pentacyclic ring E hetero-oxindole alkaloids (47) and the tetracyclic corynantheine types (48). In each table the alkaloids are listed alphabetically (ignoring prefixes). The configuration at the spiro-carbon atom, C(7), is designated[42f] either *R* [*i.e.*, (49)] or *S* [*i.e.*,(50)]. The stereochemistry at C(15) is not specified since the hydrogen atom at this position is always α.



(51) (52)

[42] [a] A. F. Beecham, N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 491; [b] M. Shamma, R. J. Shine, I. Kompiš, T. Sticzay, F. Morsingh, J. Poisson, and J. Pousset, *J. Amer. Chem. Soc.*, 1967, **89**, 1739; [c] A. H. Beckett, D. Dwuma-Badu, and R. E. Haddock, *Tetrahedron*, 1969, **25**, 5961; [d] W. F. Trager, C. M. Lee, J. D. Phillipson, R. E. Haddock, D. Dwuma-Badu, and A. H. Beckett, *Tetrahedron*, 1968, **24**, 523; [e] M. Shamma and K. F. Foley, *J. Org. Chem.*, 1967, **32**, 4141.

Table 1 *Pentacyclic oxindole alkaloids, type* (47)

R^9	R^{10}	R^{11}	R^{12}	C(7)	C(3)-H	C(20)-H	C(19)-H	*Name*
2 × *ortho*-MeO at ?				?	?	?	?	Alkaloid V[1c]
H	MeO	MeO	H	*R*	α	α	β	Carapanaubine[42b]
H	MeO	MeO	H	*S*	α	α	β	Isocarapanaubine[42f]
H	H	MeO	H	?	?	α	β	Erycinine[42g]
H	H	H	H	*R*	α	β	α	Formosanine[42a,b] (= Uncarine B)
H	H	H	H	*S*	α	β	α	Isoformosanine[42b]
H	H	H	H	?	?	?	?	Gambirdine[42i]
H	H	H	H	?	?	?	?	Isogambirdine[42i]
H	MeO	MeO	H	*S*	α	β	β	Herbaline[42h] (16,17-dihydro; C(16)–H : α)
H	H	MeO	MeO	*R*	α	α	β	Majdine[42j]
H	H	MeO	MeO	*S*	α	α	β	Isomajdine[42j]
H	H	H	H	*R*	α	β	β	Mitraphylline[42a,b]
H	H	H	H	*S*	α	β	β	Isomitraphylline[42a,b]
H	H	H	H	*R*	α	α	β	Pteropodine[42a,b,k] (= Uncarine C)
H	H	H	H	*S*	α	α	β	Isopteropodine[42a,b,k] (= Uncarine E)
H	H	H	H	*R*	α	α	α	Rauniticine-*allo*-oxindole B[42b]
H	H	H	H	*S*	α	α	α	Rauniticine-*allo*-oxindole A[42b]
H	H	H	H	*R*	β	α	α	Rauniticine-*epiallo*-oxindole B[42b]
H	H	H	H	*S*	β	α	α	Rauniticine-*epiallo*-oxindole A[42b]
H	MeO	MeO	H	*R*	β	α	β	Rauvoxine[42b]
H	MeO	MeO	H	*S*	β	α	β	Rauvoxinine[42b,e,l]
H	H	H	H	*S*	β	α	β	Speciophylline[42a] (= Uncarine D)
H	H	H	H	*S*	α	β	α	Uncarine A[42a]
H	H	H	H	*R*	β	α	β	Uncarine F[42a]
H	H	MeO	H	?	α	?	?	Vinerine[42m]
H	H	MeO	H	?	β	?	?	Vineridine[42m]

[42] [f] J. Poisson and J. L. Pousset, *Tetrahedron Letters*, 1967, 1919; [g] N. Abdurakhimova, Sh. Z. Kasimov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 135 (*Chem. Abs.*, 1968, **69**, 67587*q*); [h] I. Ognyanov, B. Pyuskyulev, M. Shamma, J. A. Weiss, and R. J. Shine, *Chem. Comm.*, 1967, 579; [i] K. C. Chan, *Tetrahedron Letters*, 1968, 3403; [j] I. Ognyanov, B. Pyuskyulev, I. Kompiš, T. Sticzay, G. Spiteller, M. Shamma, and R. J. Shine, *Tetrahedron*, 1968, **24**, 4641; [k] K. C. Chan, *Phytochemistry*, 1969, **8**, 219; [l] C. Pascard-Billy, *Bull. Soc. chim. France*, 1968, 3289; [m] Sh. Z. Kasymov, P. Kh. Yuldashev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1966, **2**, 260 (*Chem. Abs.*, 1967, **66**, 2673*n*).

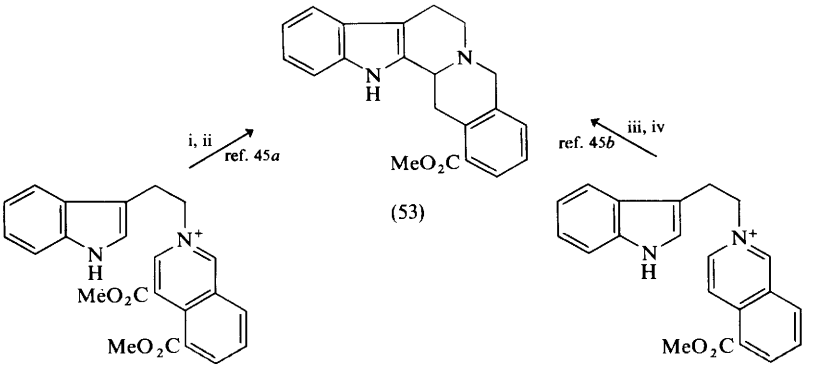
Table 2 *Tetracyclic oxindole alkaloids, type* (48)

R^9	C(7)	C(3)-H	C(20)-R	C(20)-H	*Name*
MeO	*R*	α	Et	β	Ciliaphylline[42c,d]
H	*S*	α	$CH:CH_2$	β	Corynoxeine[42n]
H	*S*	α	Et	α	Corynoxine[42c]
H	*R*	α	Et	α	Corynoxine B[42c]
MeO	*R*	α	Et	α	Mitragynine oxindole B[42c]
MeO	*S*	α	Et	β	Rhynchociline[42c,d]
H	*R*	α	Et	β	Rhynchophylline[42c]
H	*S*	α	Et	β	Isorhynchophylline[42c]
HO	*S*	α	Et	β	Rotundifoline[42c,d]
HO	*R*	α	Et	β	Isorotundifoline[42c,d]
MeO	*R*	α	$CH:CH_2$	β	Specionoxeine[42d]
MeO	*S*	α	$CH:CH_2$	β	Isospecionoxeine[42d]

In an attempt to arrive at an intermediate suitable for elaboration into 19,20-dehydroyohimbine, the unsaturated aldehyde (51) was treated with methyl acetoacetate. A mixture of epimers (52) was obtained[43] (see also ref. 44).

(±)-Dihydrogambirtannine (53) has been synthesised in two ways[45a,b] from 2-(3-indolyl)ethylisoquinolinium salts (Scheme 6).

Full details[46] of Szántay's synthesis of yohimbine[1c] have been given. An



Scheme 6

Reagents: i, H_2–Pd; ii, OH^-–H_2O; iii, $NaBH_4$–NaCN; iv, H^+–H_2O.

[42] [n] E. E. van Tamelen, J. P. Yardley, and M. Miyano, *Tetrahedron Letters*, 1963, 1011.

[43] F. E. Ziegler and J. G. Sweeny, *J. Org. Chem.*, 1969, **34**, 3545.

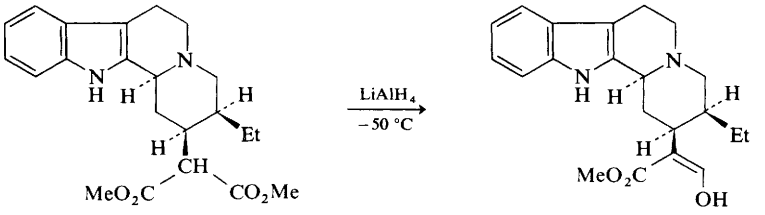
[44] [a] E. Winterfeldt, H.-E. Radunz, and T. Korth, *Chem. Ber.*, 1968, **101**, 3172; [b] E. Winterfeldt, A. J. Gaskell, T. Korth, H.-E. Radunz, and M. Walkowiak, *Chem. Ber.*, 1969, **102**, 3558.

[45] [a] E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Amer. Chem. Soc.*, 1968, **90**, 5251; [b] J. A. Beisler, *Tetrahedron*, 1970, **26**, 1961; [c] see also R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron*, 1963, **19**, 247.

[46] L. Töke, K. Honty, and C. Szántay, *Chem. Ber.*, 1969, **102**, 3248.

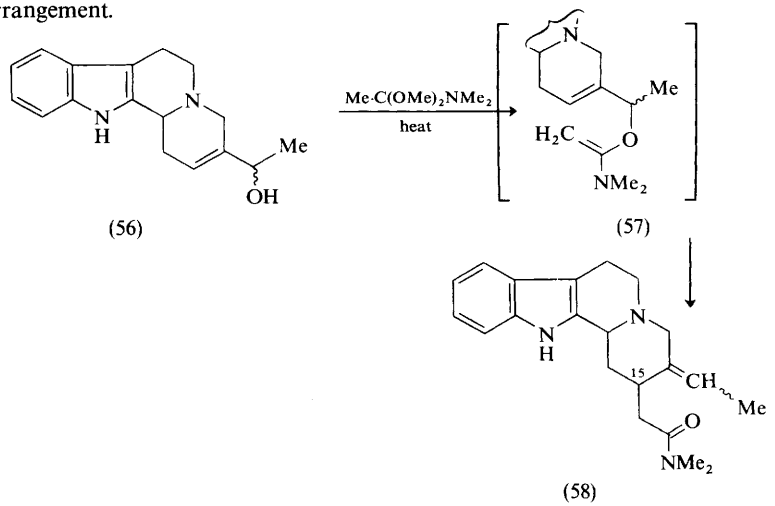
impressive series of papers[47] describe in detail van Tamelen's biogenetically-patterned synthetic accomplishments in the field of yohimbine, heteroyohimbine, and related oxindole alkaloids.[1c,d,e]

A synthesis of (−)-corynantheidine has been reported[48] which utilises an approach similar to that used previously.[1c] A crucial step, which improves on the previous sequence, is the partial reduction of the di-ester (54) to the aldehydo-ester (55); the necessity for having to introduce an aldehyde group is thereby avoided.



(54) (55)

A synthesis of (±)-dihydrocorynantheol and its *C*(3)-epimer incorporates a very neat step to introduce the *C*(15)-substituent.[49] The allyl alcohol (56), easily synthesised *via* Ban's procedure, was treated with *NN*-dimethylacetamide dimethyl acetal giving (58), presumably by way of the species (57) and a Claisen rearrangement.



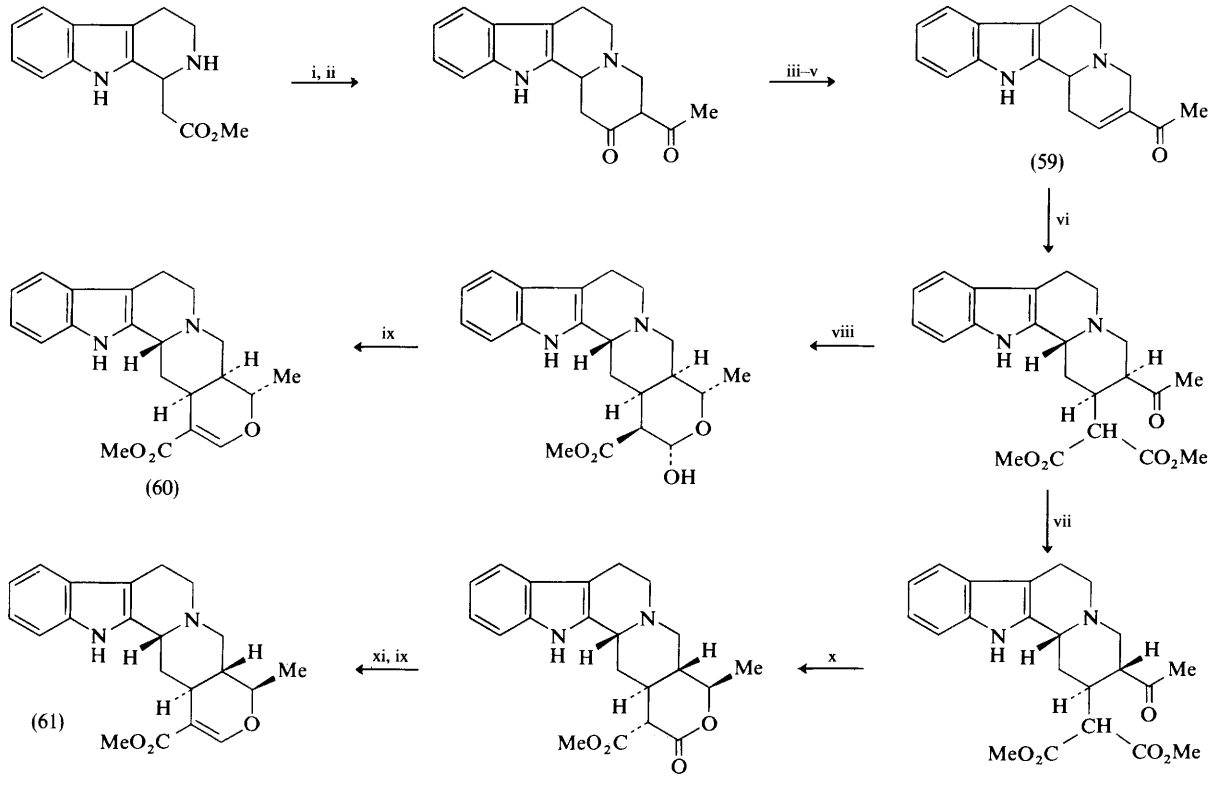
(56) (57)

(58)

[47] E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Amer. Chem. Soc.*, 1969, **91**, 7315; E. E. van Tamelen, J. P. Yardley, M. Miyano, and W. B. Hinshaw, jun., *ibid.*, 1969, **91**, 7333; E. E. van Tamelen and J. B. Hester, jun., *ibid.*, 1969, **91**, 7342; E. E. van Tamelen and I. G. Wright, *ibid.*, 1969, **91**, 7349; E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, *ibid.*, 1969, **91**, 7359.

[48] C. Szántay and M. Bárczai-Beke, *Chem. Ber.*, 1969, **102**, 3963.

[49] F. E. Ziegler and J. G. Sweeny, *Tetrahedron Letters*, 1969, 1097.

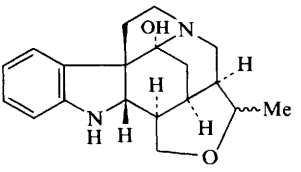


Scheme 7

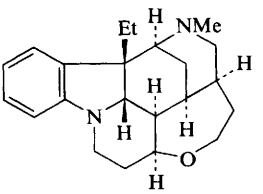
Reagents: i, CH_2:CH·COMe; ii, Bu^{t}OK; iii, $POCl_3$–DMF; iv, $LiAl(Bu^tO)_3H$; v, aq. H_2SO_4; vi, MeO^-–$CH_2(CO_2Me)_2$; vii, MeO^-; viii, $NaBH_4$ at −30 °C; ix, PPA; x, H_2–Pt–AcOH; xi, $NaBH_4$.

Syntheses of (±)-akuammigine,[44a] (±)-tetrahydroalstonine,[44a] (±)-ajmalicine,[44b] (±)-3-iso-19-epiajmalicine,[44b] and the oxindoles (±)-formosanine[44b] and (±)-isoformosanine,[44b] obtained by oxidative rearrangement of 3-iso-19-epi-ajmalicine, have been carried out starting with the key ketone (59). Scheme 7 illustrates how the product of either kinetic or thermodynamic control of the addition of malonate to this ketone can be used to synthesise D/E *cis*-alkaloids [*e.g.*, akuammigine (60)] or D/E *trans*-alkaloids [*e.g.*, 3-iso-19-epi-ajmalicine (61)].

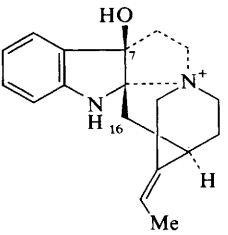
Strychnine–Akuammicine–Condylocarpine–Uleine Group. Several variations of the strychnosplendine (62) theme isolated from *Strychnos splendens* have been examined in detail.[50] A careful investigation[51] has elucidated the complete pathway by which strychnine or its metho-salt can be degraded to the Wieland–Gumlich aldehyde or its metho-salt. Sodium–ammonia cleavage of dihydrostrychnidine A methosulphate gives[52] (63).



(62)



(63)

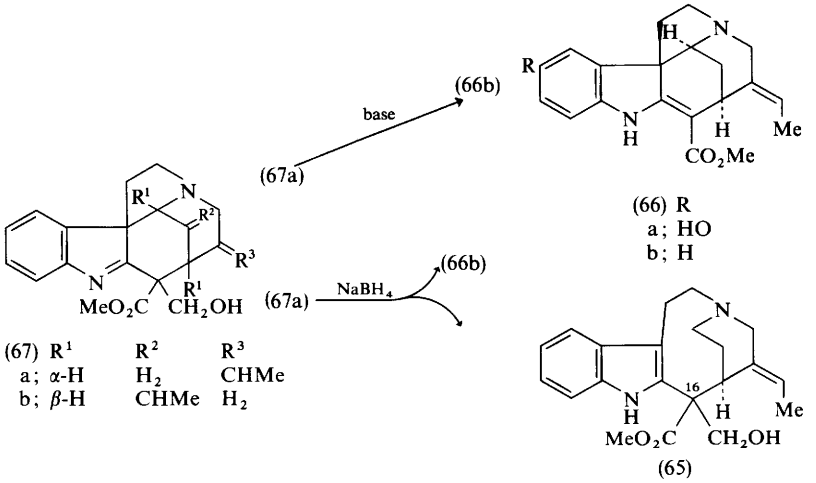


(64)

An *X*-ray analysis of hunteracine from *Hunteria eburnea* shows it to be a salt (64) of a novel type.[53] Its relationship to the other alkaloids of this group can be seen by assuming the loss of the *C*(16)-substituents of stemmadenine (65) and *C*(7)-hydroxylation, followed by nucleophilic closure of the basic nitrogen on to the indole α-position.

[50] M. Koch, M. Plat, and J. Le Men, *Tetrahedron*, 1969, **25**, 3377.
[51] J. R. Hymon, H. Schmid, P. Karrer, A. Boller, H. Els, P. Fahrni, and A. Fürst, *Helv. Chim. Acta*, 1969, **52**, 1564.
[52] O. Achmatowicz and J. Szychowski, *Roczniki Chem.*, 1969, **43**, 699 (*Chem. Abs.*, 1969, **71**, 70784y).
[53] R. H. Burnell, A. Chapele, M. F. Khalil, and P. H. Bird, *Chem. Comm.*, 1970, 772.

Sewarine, from *Rhazya stricta*, was shown to be 10-hydroxyakuammicine (66a) by spectral comparison with akuammicine (66b) and with other A ring oxygenated indole alkaloids.[54] Preakuammicine (67a), an isomer of precondylocarpine (67b), has been isolated from young *Vinca rosea* seedlings.[55a] The retroaldol loss of formaldehyde and the formation of akuammicine was base catalysed. Borohydride reduction, as well as causing some retroaldolisation, gave rise to stemmadenine[55b] (65).

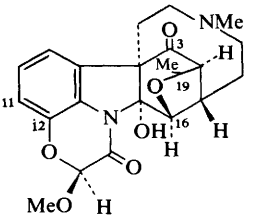


Dichotine (68a) and 11-methoxydichotine, bases isolated from *Vallesia dichotoma*, have structures incorporating several interesting features.[55c] The absence of a bond between C(3) and N_b places them in the same relationship to alkaloids of the aspidospermatidine type as N_b-methylpseudostrychnine bears to strychnine; the C(12)–N_a heterocyclic ring is similar to those in the obscurinervine types but the ether link between C(16) and C(19) is novel. The *X*-ray analysis of the hydrobromide of dichotine, by which the overall structure was established, showed that the transannular N_b–C(3)-carbonyl interaction, evidenced by the spectra of the free base, results in carbonyl oxygen protonation, the salt having a full bond between N_b and C(3).

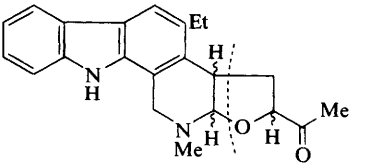
Subincanine, a pentacyclic carbazole alkaloid isolated from *Aspidosperma subincanum*, has been assigned[55d] structure (68b) as a working hypothesis, on the basis of its spectra, cleavage of the N–C–O system by reduction with sodium borohydride, and co-occurrence with alkaloids of the uleine (73b) type; the portion of the molecule to the left of the dotted line has the same carbon skeleton

[54] Y. Ahmad, P. W. Le Quesne, and N. Neuss, *Chem. Comm.*, 1970, 538.

[55] [a] A. I. Scott, P. C. Cherry, and A. A. Qureshi, *J. Amer. Chem. Soc.*, 1969, **91**, 4932; [b] *ibid.*, 5874; [c] N. C. Ling, C. Djerassi, and P. G. Simpson, *J. Amer. Chem. Soc.*, 1970, **92**, 222; [d] A. J. Gaskell and J. A. Joule, *Tetrahedron Letters*, 1970, 77.



(68a)



(68b)

as uleine. The remaining four skeletal carbon atoms are a novelty and the alkaloid, whatever its structure may finally prove to be, poses interesting biogenetic questions.

The tetracyclic ketone[56a,b] (69), synthesised from tryptamine in six steps, has been used in syntheses of (±)-tubifoline,[56b] (±)-tubifolidine,[56b] (±)-condyfoline,[56b] (±)-geissoschizoline,[56c] and (±)-tubotaiwine.[56d] Scheme 8 shows the route to geissoschizoline[56c] (70) and the interesting skeletal rearrangement which occurred when the alcoholic intermediate (71) was treated with trifluoroacetic anhydride to give (72).

Two approaches[57] to the (±)-dasycarpidone–3-epi-dasycarpidone system (73a) have been published (Scheme 9) and the ketones have been transformed[57b] into the isomeric (±)-uleines (73b). In one synthesis,[57a] a 2-oxopiperidine-4-ester (74) was neatly linked to the indole 3-position by trapping the unstable salt from a Vilsmeier reaction by reduction with borohydride. Polyphosphoric acid brought about cyclisation of the corresponding acid (75) to a mixture of the dasycarpidones. The other approach[57b] utilised a 2-isonicotinoyl indole (76); partial reduction of its methiodide left one double bond in the piperidine ring. This unsaturation was later utilised to produce an immonium function in this ring to allow ring closure on to the indole β-position.

Sarpagine–Ajmaline Group. Nuclear Overhauser effects have been demonstrated[58a] between the *C*(15)-hydrogen and the *C*(18)-hydrogens and the *C*(6)-hydrogen and the *C*(9)-hydrogen, respectively, of dehydrovoachalotine (77a) from *Voacanga chalotiana*.[58b]

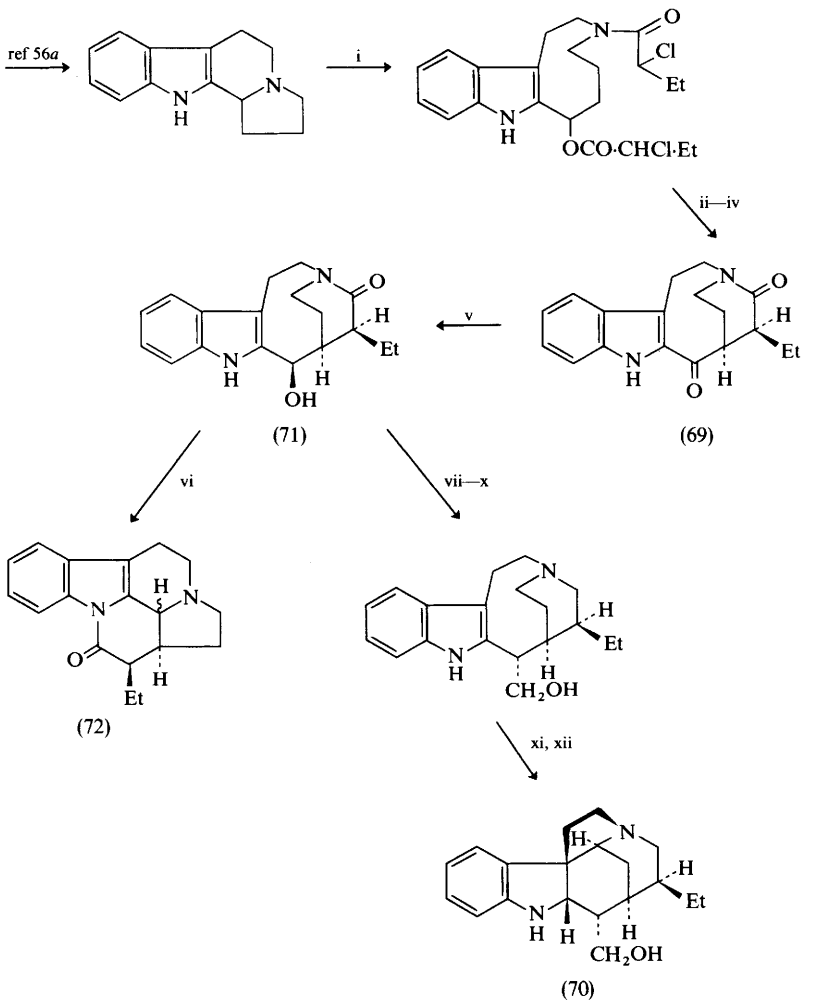
Other alkaloids of this structural type have been isolated from *Gardneria nutans*.[59] Gardnutine[59a] (77b), which is a 6-methoxyindole derivative and lacks

[56] [a] S. Corsano and S. Algieri, *Ann. Chim.* (*Italy*), 1960, **50**, 75; [b] B. A. Dadson, J. Harley-Mason, and G. H. Foster, *Chem. Comm.*, 1968, 1233; [c] B. A. Dadson and J. Harley-Mason, *Chem. Comm.*, 1969, 665; [d] *ibid.*, p. 665; [e] J. Harley-Mason and C. G. Taylor, *ibid.*, 1384.

[57] [a] L. J. Dolby and H. Biere, *J. Amer. Chem. Soc.*, 1968, **90**, 2699; [b] A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc.* (*C*), 1969, 2738.

[58] [a] J. C. Nouls, P. Wollast, J. C. Braekman, G. Van Binst, J. Pecher, and R. H. Martin, *Tetrahedron Letters*, 1968, 2731; [b] C. Tirions, M. Kaisin, J. C. Braekman, J. Pecher, and R. H. Martin, *Chimia* (*Switz.*), 1968, **22**, 87.

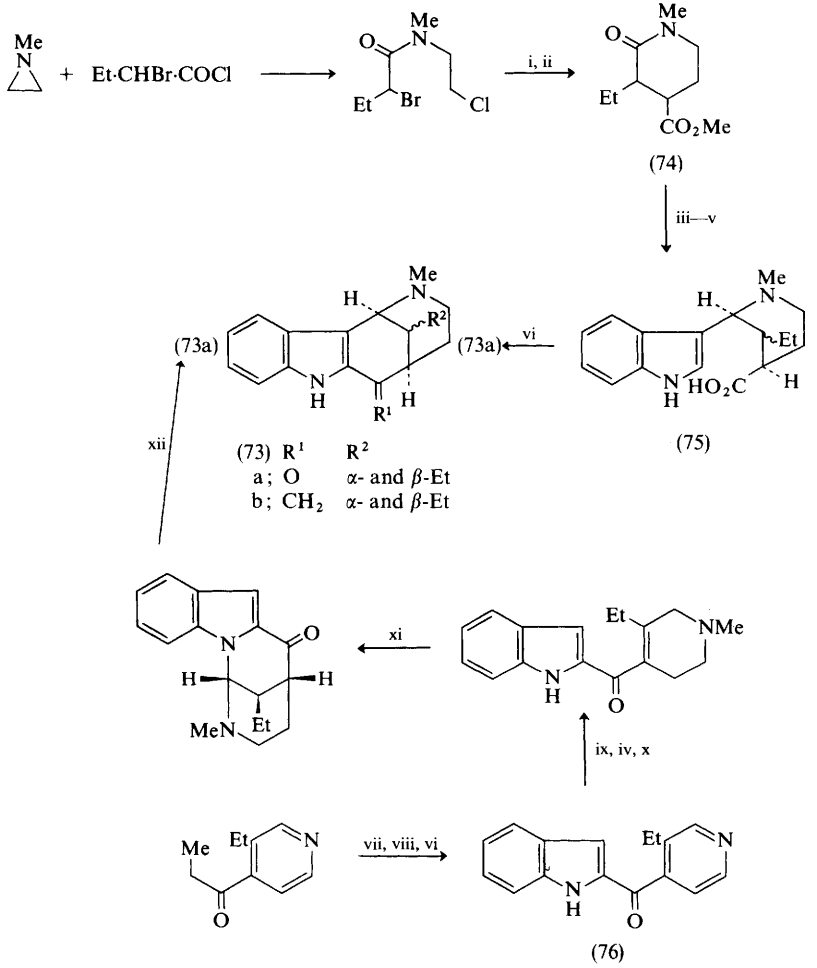
[59] [a] S. Sakai, A. Kubo, and J. Haginiwa, *Tetrahedron Letters*, 1969, 1485; [b] S. Sakai, A. Kubo, T. Hamamoto, M. Wakabayashi, K. Takahashi, Y. Ohtani, and J. Haginiwa, *ibid.*, 1489; [c] A. Kubo, *J. Pharm. Soc. Japan*, 1970, **90**, 224 (*Chem. Abs.*, 1970, **72**, 121750*q*).



Scheme 8

Reagents: i, $(Et{\cdot}CHCl{\cdot}CO)_2O$; ii, NaOH; iii, MnO_2; iv, $Et{\cdot}CMe_2ONa$; v, $NaBH_4$; vi, $(CF_3CO)_2O$; vii, Ac_2O; viii, NaCN in DMSO; ix, $c{\cdot}H_2SO_4$–MeOH; x, $LiAlH_4$; xi, O_2–Pt; xii, B_2H_6.

a methoxycarbonyl function, co-occurs with gardnerine (78) and hydroxygardnutine (79), and the three alkaloids have been interrelated[59a] (Scheme 10). Their overall structures and absolute stereochemistry were established by chemical reactions[59] and the conversion of gardnerine into 17,21-dideoxy-1-demethyl-1,2-dihydroajmaline.[59a]

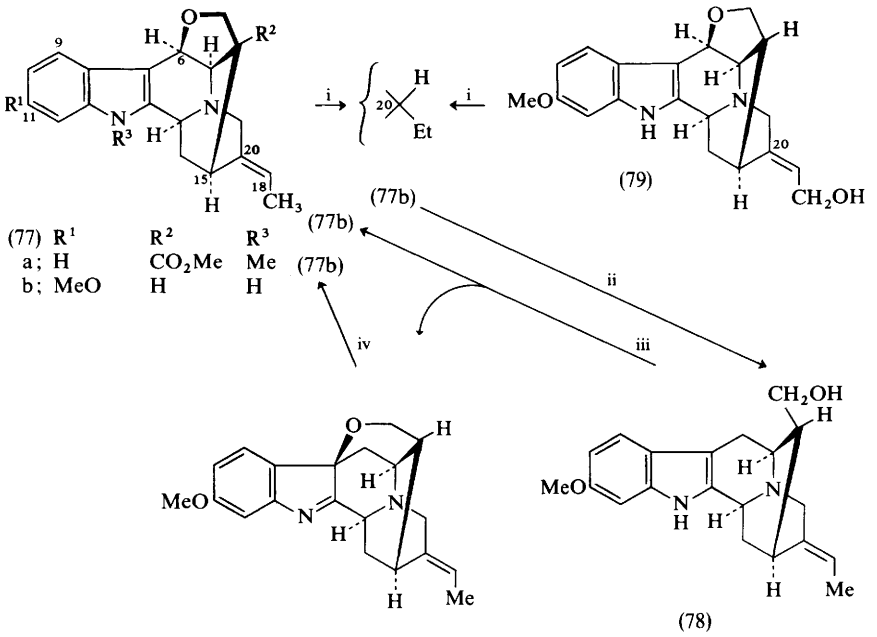


Scheme 9

Reagents: i, $CH_2(CO_2Me)_2$–MeO^-; ii, NaI–AcOH; iii, indole–$POCl_3$; iv, $NaBH_4$; v, NaOH; vi, PPA; vii, pyrrolidine–TsOH; viii, PhN_2^+; ix, MeI; x, MnO_2; xi, $MeSOCH_2Na$; xii, AcOH.

Taberpsychine[60a] from *Tabernaemontana psychotrifolia* and anhydrovobasinol[60b] from *Conopharyngia durissima* have been assigned the same structure (80). Anhydrovobasinol was partially synthesised from vobasine diol by acid-catalysed dehydrative ring closure.

[60] [a] P. R. Benoin, R. H. Burnell, and J. D. Medina, *Tetrahedron Letters*, 1968, 807; [b] J. J. Dugan, M. Hesse, U. Renner, and H. Schmid, *Helv. Chim. Acta*, 1969, **52**, 701.



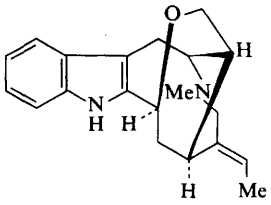
Scheme 10

Reagents: i, H_2–Pt; ii, $LiAlH_4$; iii, CrO_3–H_2SO_4; iv, H^+.

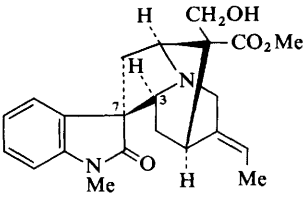
Demethoxycarbonyl-19,20-dihydrovobasine has been isolated[61] from *Rauwolfia discolor* and 17-*O*-benzoylvincamajine from *Alstonia macrophylla*.[62]

Another alkaloid from *Voacanga chalotiana* is the first example of an oxindole alkaloid with a sarpagine-type aliphatic skeleton. Analysis of the spectra of voachalotine oxindole led to the formulation (81) and this was verified by its partial synthesis, by the treatment of voachalotine with aqueous potassium dichromate.[63] The stereochemistry at C(7) was deduced from the observation of a hydrogen-bonded oxindole carbonyl-group absorption in the i.r. spectrum of the alkaloid salt but not in that of the free base; this is only possible for the configuration (81) shown. Interestingly, no epimerisation at C(7)–C(3) was observed under the conditions which normally effect such changes in the heteroyohimbine–corynantheine oxindole alkaloids. In this case an analogous mechanism of epimerisation would require the formation of a bridgehead immonium grouping.

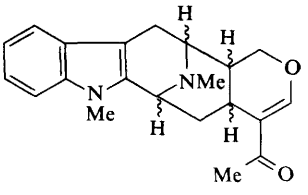
[61] G. Combes, L. Fonzes, and F. Winternitz, *Phytochemistry*, 1968, **7**, 477.
[62] B. Mukherjee, A. B. Ray, A. Chatterjee, and B. C. Das, *Chem. and Ind.*, 1969, 1387.
[63] J. C. Braekman, M. Tirions-Lampe, and J. Pecher, *Bull. Soc. chim. belges*, 1969, **78**, 523.



(80)



(81)



(82)

Alstonerine[64a] from *Alstonia muelleriana* (82) is a structural type first recognised as one half of the dimeric indole alkaloid villalstonine. The oxindole analogue[64b] of this structural type has been known for some time.

The tetracyclic ketone[65a] (83) has been elaborated,[65b] *via* an intermediate in Masamune's synthesis,[1f] into ajmaline, and also used to derive (±)-isoajmaline[65c] (84a) (Scheme 11).

van Tamelen has successfully developed another biogenetically-patterned total synthesis (Scheme 12), this time of deoxyajmalal A[66a] (85), which has been previously converted[66b] into ajmaline (84b). Many of the steps are of a type typical of van Tamelen's syntheses and of proven reliability. The novelty in this particular synthesis is in the ingenious use of the oxidative decarboxylation of the tryptophan residue, which provides the activation necessary for forming the C(5)–C(16) bond [(86) → (87)], a process which may well parallel the making of this bond in nature.[66c]

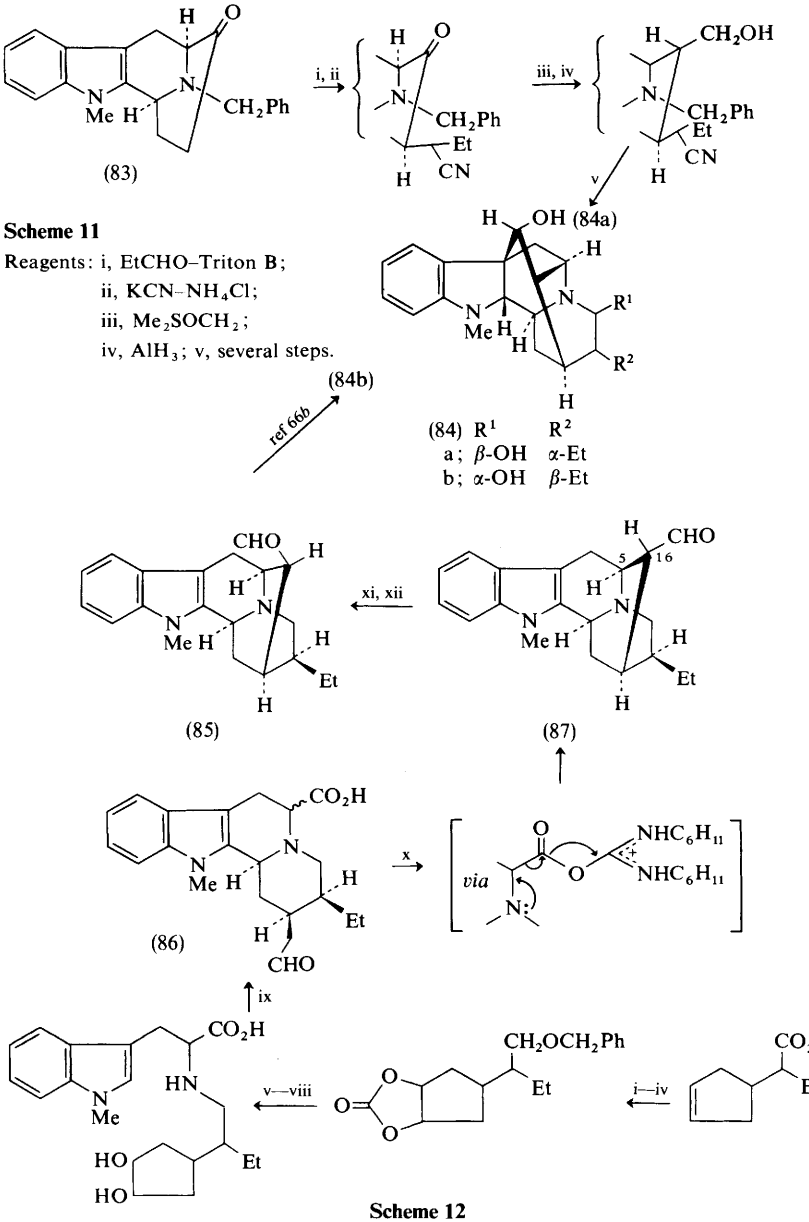
Aspidospermine–Aspidofractine Group. An *X*-ray analysis[67a] of the N_a-hydriodide of (±)-deacetylaspidospermine has verified the prediction[67b] that the piperidine ring has a chair conformation and not a boat conformation as it has in the N_b-metho-salt used in the original structure determination.

[64] [a] J. M. Cook, P. W. Le Quesne, and R. C. Elderfield, *Chem. Comm.*, 1969, 1306; [b] C. E. Nordman and K. Nakatsu, *J. Amer. Chem. Soc.*, 1963, **85**, 353.

[65] [a] N. Yoneda, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1231; [b] K. Mashimo and Y. Sato, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 353; [c] K. Mashimo and Y. Sato, *Tetrahedron*, 1970, **26**, 803.

[66] [a] E. E. v. Tamelen and L. K. Oliver, *J. Amer. Chem. Soc.*, 1970, **92**, 2136; [b] M. F. Bartlett, B. F. Lambert, H. M. Werblood, and W. I. Taylor, *J. Amer. Chem. Soc.*, 1963, **85**, 475; J. D. Hobson and J. G. McCluskey, *J. Chem. Soc.* (*C*), 1967, 2015; [c] E. E. v. Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, 1968, **24**, 687.

[67] [a] N. Sakabe, Y. Sendo, I. Iijima, and Y. Ban, *Tetrahedron Letters*, 1969, 2527; [b] G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, 1960, 1463.

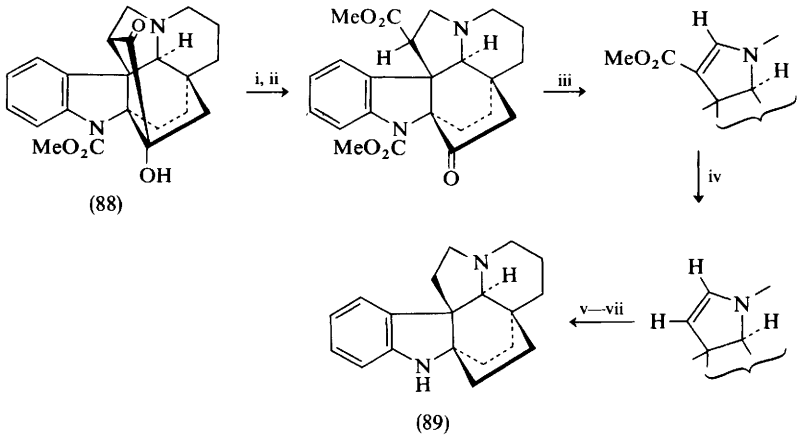


Scheme 11

Reagents: i, EtCHO–Triton B;
ii, KCN–NH_4Cl;
iii, Me_2SOCH_2;
iv, AlH_3; v, several steps.

Scheme 12

Reagents: i, $LiAlH_4$; ii, $PhCH_2Cl$–KOH; iii, OsO_4–pyridine; iv, $(MeO)_2CO$–MeO^-; v, H_2–Pd; vi, CrO_3–pyridine; vii, N_a-methyltryptophan–H_2–Pd/C; viii, KOH; ix, $NaIO_4$–NaOAc; x, DCC–TsOH; xi, resolve *via* D-camphor-10-sulphonate; xii, equilibrate in AcOH–NaOAc.



Scheme 13

Reagents: i, $NaIO_4$; ii, MeOH–HCl; iii, CrO_3–pyridine; iv, 2N-HCl; v, Zn–H_2SO_4; vi, Zn–Hg–HCl; vii, NaOH.

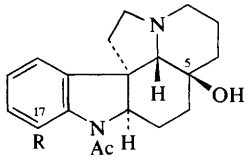
(−)-Kopsine (88) has been degraded[68] to (−)-aspidofractinine (89) (Scheme 13). All the alkaloids with aspidofractinine skeleta have the same absolute configuration.

A group of bases with various *C*(17)- and N_a-substituents in an aspidospermine skeleton have been obtained from *Aspidosperma cylindrocarpon*,[69] in which the *C*(5)-side chain occurs as $CHOH{\cdot}CO_2Me$ or CH_2CO_2Me. 6,7-Epoxy-20-hydroxytabersonine types have been obtained from *Catharanthus lanceus*[70] and N_a-formylkopsinol from *A. verbascifolium*.[71]

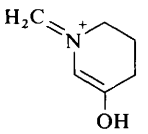
A. dispermum has yielded[72a] two very interesting alkaloids, (90a) and (90b), in which the usual two-carbon *C*(5)-substituent is not present, and in these bases it is replaced by a hydroxy-group. Spectral data for these bases, including typical aspidospermine fragmentation (see below, however), *e.g.* peaks at *m/e* 112 and 140, owing to (91) and (92) respectively, led to the positioning of the hydroxy-group at C(5); this was confirmed by an *X*-ray analysis[72b] of 17-*O*-methyl-aspidodispermine (90c) hydrobromide. These alkaloids have the same relative and absolute stereochemistry as aspidospermine.

Vallesamidine[73] (93) from *Vallesia dichotoma* is another novel variant on the aspidosperma theme; its structure was derived by *X*-ray analysis of its methiodide.

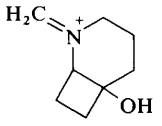
[68] A. Guggisberg, A. A. Gorman, B. W. Bycroft, and H. Schmid, *Helv. Chim. Acta*, 1969, **52**, 76.
[69] B. V. Milborrow and C. Djerassi, *J. Chem. Soc.* (*C*), 1969, 417.
[70] D. J. Abraham, N. R. Farnsworth, W. D. Loub, and R. N. Blomster, *J. Org. Chem.*, 1969, **34**, 1575.
[71] J. C. Braekman, C. Hootele, C. Van Moorleghem, M. Kaisin, J. Pecher, L. D. Antonaccio, and B. Gilbert, *Bull. Soc. chim. belges*, 1969, **78**, 63.
[72] [a] M. Ikeda and C. Djerassi, *Tetrahedron Letters*, 1968, 5837; [b] N. C. Ling and C. Djerassi, *Tetrahedron Letters*, 1970, 3015.
[73] S. H. Brown, C. Djerassi, and P. G. Simpson, *J. Amer. Chem. Soc.*, 1968, **90**, 2445.



(90) R
a; H
b; HO
c; MeO

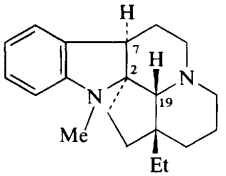


(91)

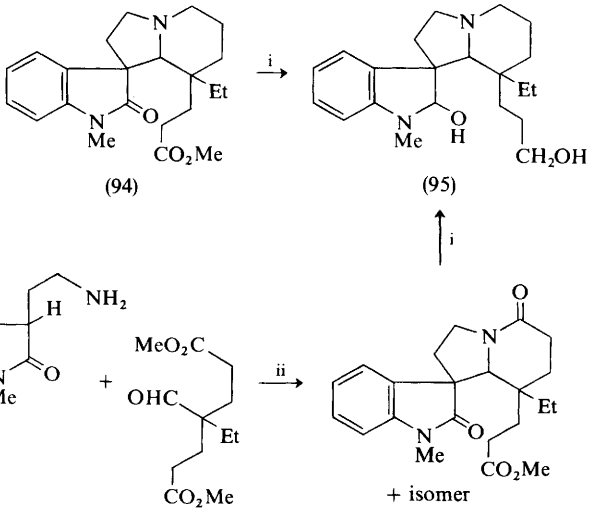


(92)

Its relationship to the standard skeleton can be seen by visualising a migration of C(19) from C(7) to C(2). A significant warning accompanied the spectral data on this alkaloid. Its mass spectrum showed the 'typical' fragmentation of the pentacyclic aspidospermine types, *i.e.* $M - 28$ and *m/e* 124, so that these features alone cannot be taken as diagnostic of the aspidospermine skeleton.



(93)



Scheme 14

Reagents: i, $LiAlH_4$; ii, NaOAc.

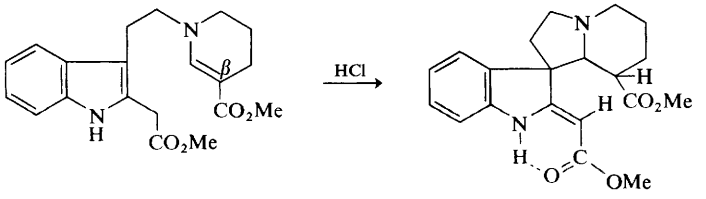
The structure[74] (94) for vincatine from *Vinca minor* was arrived at by mass spectral examination of the alkaloid and its lithium aluminium hydride reduction product (95), which has since been synthesised[75] (Scheme 14). It is the first oxindole alkaloid with an aspidospermine aliphatic skeleton.

Quite different lines of approach to the synthesis of the aspidospermine nucleus have been reported recently.[45a,76] In one route,[45a] the product (96) of Mannich condensation (initial β-protonation of the enamine system) at the indole β-position of a β-substituted indole was isolated.[45c] This approach has wide implications, both mechanistic and biogenetic, and succeeded because the indole α-substituent (CH_2CO_2Me) provided, by isomerisation, a hydrogen-bonded enamino-acrylate unit to stabilise the substitution product (96).

The second synthesis[76] of a model system is summarised in Scheme 15. Two novel aspects of this sequence merit comment. Firstly, the cyclisation (97) → (98), which occurred during the hydrogenation step, presumably involved a transient, partially reduced pyridinium species, which effected an intramolecular Mannich condensation. Secondly, the insertion of the tryptamine two-carbon bridge (99) → (100) was brought about in a manner which had not been successfully used previously.

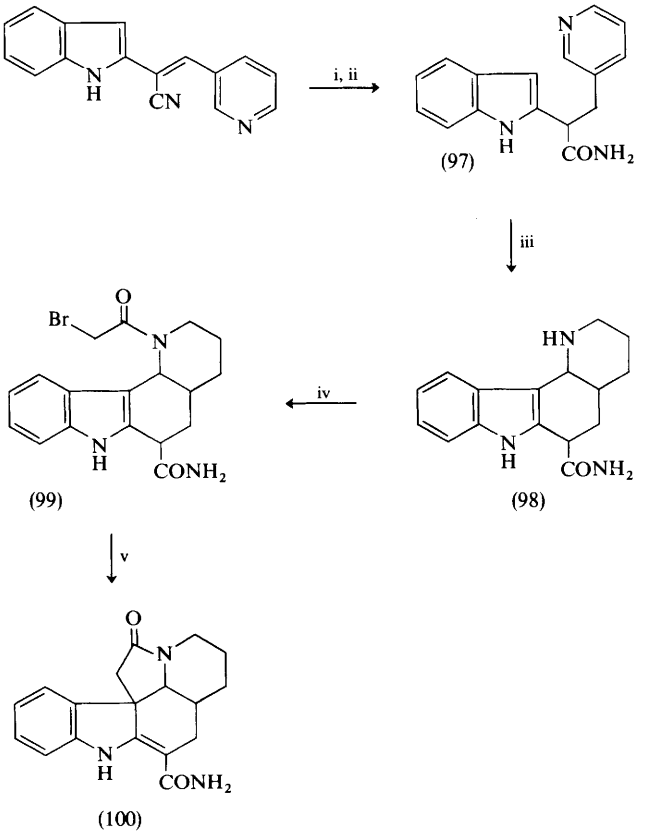
A careful examination[77a,b] of the stereochemistry of the systems (101a) has shown that the stereochemistry assigned to the crucial intermediate, of this overall structure, in previous syntheses of aspidospermine was incorrect. Thus the Stork intermediate (101b) has a *cis* C/D ring junction and it is now not necessary to postulate epimerisation at C(19) during Fischer cyclisation to the aspidospermine system. The genuine isomer (101c) has been converted,[77c] by a reductive Fischer cyclisation of its 2-methoxyphenylhydrazone with formic acid, into a (±)-isomer of deacetylaspidospermine, in which the C/D ring junction is *trans*.

A synthesis[78a] (Scheme 16) of (±)-quebrachamine (102) employs the cyclic enamine (103) which, after introduction of an acetic ester side chain by enamine



(96)

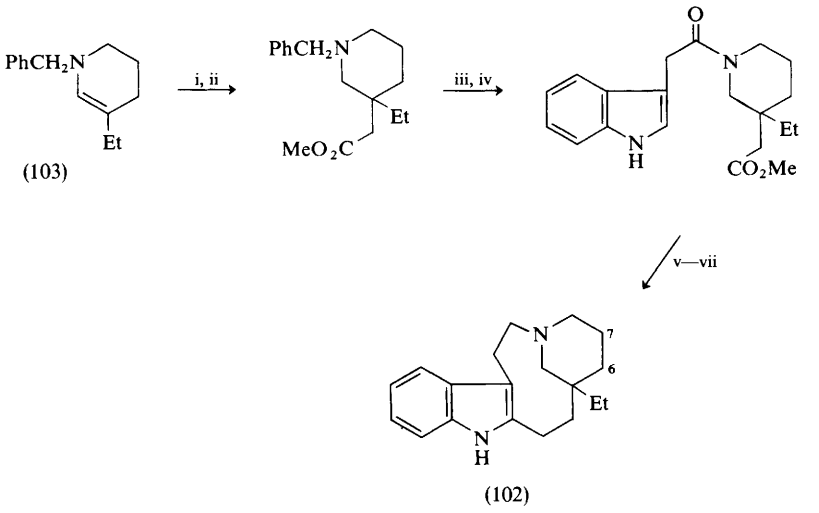
[74] L. W. Döpke, H. Meisel, and H.-W. Fehlhaber, *Tetrahedron Letters*, 1969, 1701.
[75] L. Castedo, J. Harley-Mason, and M. Kaplan, *Chem. Comm.*, 1969, 1444.
[76] H.-P. Husson, C. Thal, P. Potier, and E. Wenkert, *Chem. Comm.*, 1970, 480.
[77] [a] Y. Ban, M. Akagi, and T. Oishi, *Tetrahedron Letters*, 1969, 2057; [b] Y. Ban, I. Iijima, I. Inoue, M. Akagi, and T. Oishi, *Tetrahedron Letters*, 1969, 2067; [c] Y. Ban and I. Iijima, *ibid.*, 2523.
[78] [a] F. E. Ziegler, J. A. Kloek, and P. A. Zoretic, *J. Amer. Chem. Soc.*, 1969, **91**, 2342; [b] F. E. Ziegler and G. B. Bennett, *Tetrahedron Letters*, 1970, 2545.



Scheme 15

Reagents: i, $NaBH_4$; ii, H_2O_2–NaOH; iii, H_2–Pt–HCl; iv, $BrCH_2COBr$; v, $NaHCO_3$–DMF.

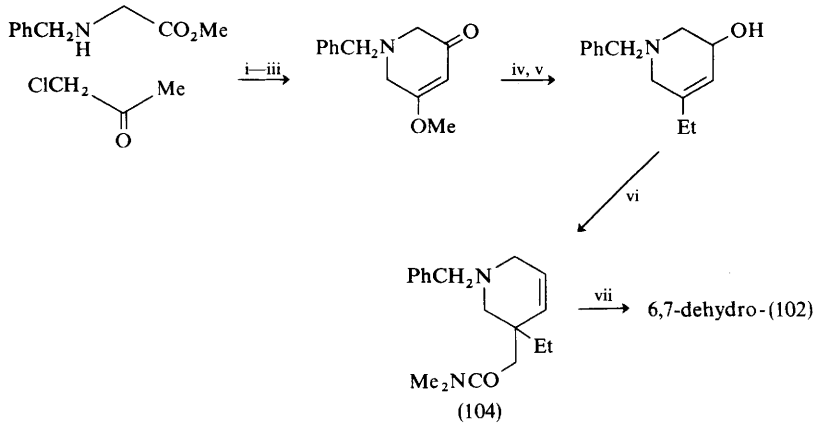
(101)	R^1	R^2	R^3
a;	Et or H	H	H
b;	β-Et	β-H	β-H
c;	β-Et	α-H	β-H



Scheme 16

Reagents: i, $BrCH_2CO_2Me$; ii, $NaBH_4$; iii, H_2–Pd/C; iv, 3-indolylacetyl chloride; v, NaOH; vi, PPA; vii, $LiAlH_4$.

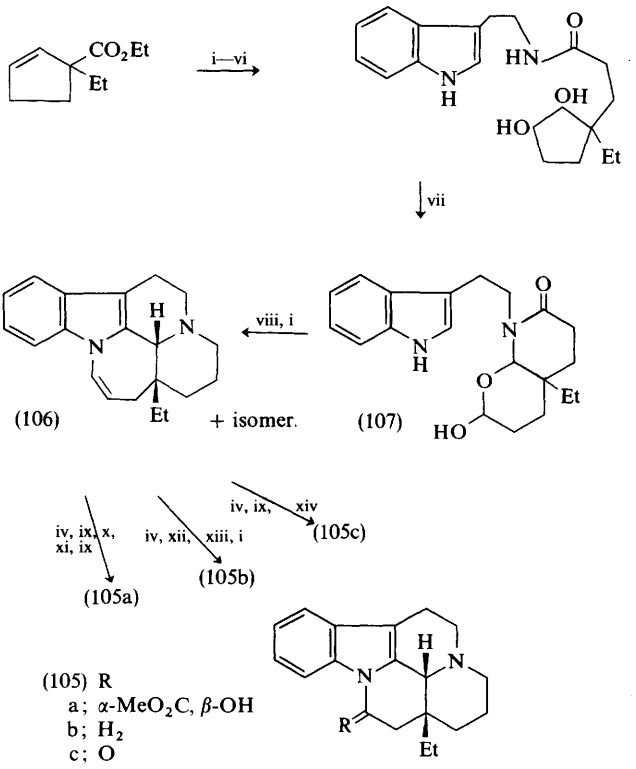
alkylation and reduction, was coupled to a 3-indolyl acetate unit and cyclised with polyphosphoric acid. A closely related synthesis[78b] employing the unsaturated piperidine derivative (104) [see also synthesis of (58)] led to the formation of (±)-6,7-dehydroquebrachamine.



Reagents: i, aq. $NaHCO_3$; ii, Bu^tO^-–Bu^tOH–Et_2O; iii, CH_2N_2; iv, EtMgBr; v, $NaBH_4$; vi, $MeC(OMe)_2NMe_2$–heat; vii, several steps.

Full details have been published[79] of Kutney's syntheses[1g] in the aspidosperma field.

Eburnamine Group. Further studies[80] of the mass spectral behaviour of eburnane derivatives have been made and the o.r.d. of eburnamenine types examined.[81]



Scheme 17

Reagents: i, $LiAlH_4$; ii, $(Bu^tO)_3Al$–*p*-benzoquinone; iii, $Ph_3P{:}CHCO_2Me$; iv, OsO_4; v, H_2–Pd–C; vi, tryptamine; vii, $NaIO_4$; viii, AcOH; ix, Me_2SO–Et_3N–pyridine–SO_3–H_2O; x, NaOH; xi, CH_2N_2; xii, $Pb(OAc)_4$; xiii, K_2CO_3; xiv, $Cu(OAc)_2$.

[79] J. P. Kutney, E. Piers, and R. T. Brown, *J. Amer. Chem. Soc.*, 1970, **92**, 1700; J. P. Kutney, W. J. Cretney, J. R. Hadfield, E. S. Hall, and U. R. Nelson, *ibid.*, 1970, **92**, 1704; J. P. Kutney, R. T. Brown, E. Piers, and J. R. Hadfield, *ibid.*, 1970, **92**, 1708; J. P. Kutney, W. J. Cretney, P. L. Quesne, B. McKague, and E. Piers, *ibid.*, 1970, **92**, 1712; J. P. Kutney, N. Abdurahman, C. Gletsos, P. L. Quesne, E. Piers, and I. Vlaltas, *ibid.*, 1970, **92**, 1727; see also J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *ibid.*, 1968, **90**, 3891.

[80] V. Kováčik and I. Kompiš, *Coll. Czech. Chem. Comm.*, 1969, **34**, 2809.

[81] K. Bláha, Z. Kobliková, and J. Trojánek, *Coll. Czech. Chem. Comm.*, 1969, **33**, 690.

A new line to the synthesis of the eburnamine type alkaloids has produced (Scheme 17) (±)-vincamine[82a] (105a), (±)-eburnamine[82b] (105b), and (±)-eburnamonine[82a] (105c). Acid-catalysed rearrangement of the carbinolamide (107) gave homoeburnamenine (106) which contained all the carbons necessary for the formation of vincamine.

Ibogamine Group. A number of 3-hydroxyindolenines,[83a–d] in some cases[83c,d] co-occurring with the corresponding ψ-indoxyl derivatives, and corresponding to known indole alkaloids of this group, have been recognised recently. In all cases the hydroxy-indolenines were synthesised from the corresponding alkaloidal indole by oxidation, with oxygen–light[83a,c,d] or hydrogen peroxide,[83b] and the indoxyls prepared[83c,d] by a subsequent base-catalysed rearrangement. Efforts to obtain the oxindole analogue of conopharyngine, isolated from *Tabernaemontana crassa*, by oxidation of the indolic alkaloid have so far failed.[84]

Synthesis in the iboga field continues to attract considerable attention and several new ways of tackling the problem have recently been published,[85–90] as have details[79] of Kutney's approach[1g] to the system.

Desethylibogamine lactam (108a) has been synthesised[85] *via* a Fischer indole synthesis using the tricyclic keto-amide (109a) which contained the complete aliphatic portion of the molecule (Scheme 18). The keto-amide was constructed from homodihydrocarbostyril (110) into which a carboxy-group was introduced at the *para*-position. After reduction of the benzene ring, cyclisation and oxidation gave the isoquinuclidine keto-amide (109a).

Another approach,[86] which has given (±)-ibogamine (108c), also utilised a final Fischer reaction, with the ketone (109b). In this synthesis the aliphatic portion of the molecule was constructed in quite a different way (Scheme 19). The monoacetal-monoxime (111) was subjected to the Beckmann rearrangement to produce the seven-membered heterocyclic ring of the alkaloid. Epoxidation followed by reduction led to (112) carrying an oxygen function at C(2), which provides a handle to introduce a functionalised C(19) for cyclisation to the isoquinuclidine (109b).

A very ingenious method[87] of producing the isoquinuclidine system has been applied to the syntheses of (±)-ibogamine[87a,b] (Scheme 20), (±)-epi-ibogamine,[87b] and (±)-coronaridine.[87b] Central to the method is the reaction of a 4-aminomethylcyclohex-1-ene [*e.g.* (113)] with lead tetra-acetate to give a bridged

[82] [a] K. H. Gibson and J. E. Saxton, *Chem. Comm.*, 1969, 1490; [b] K. H. Gibson and J. E. Saxton, *Chem. Comm.*, 1969, 799.

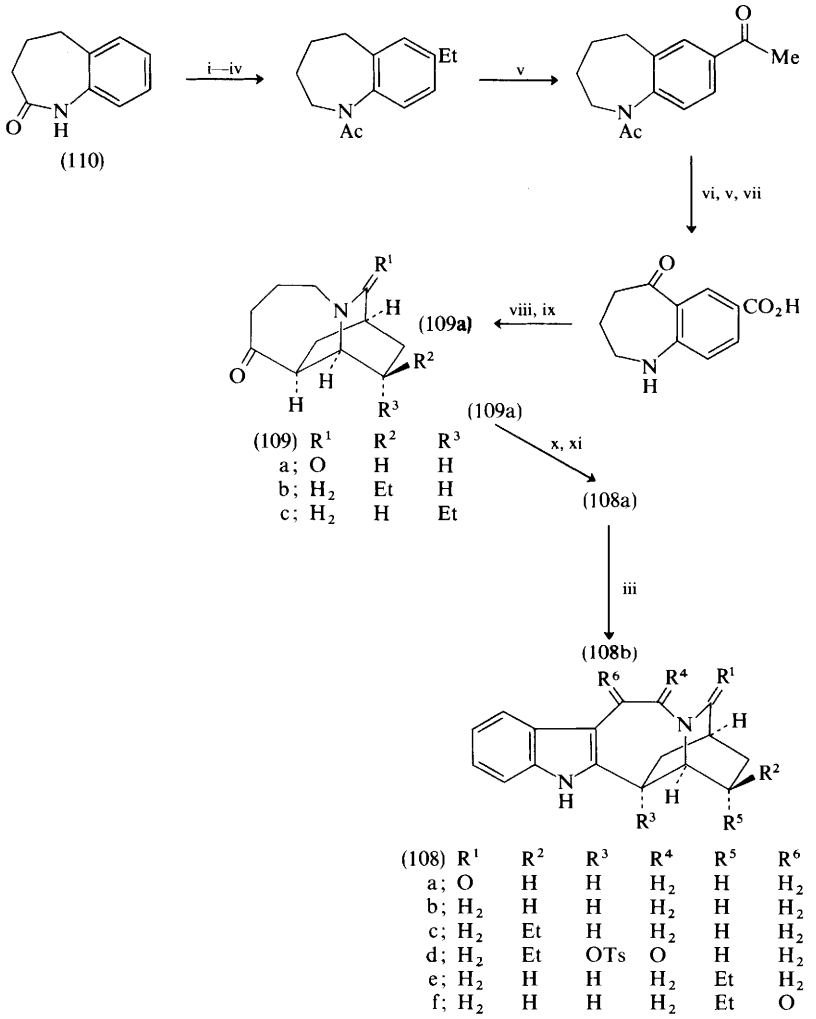
[83] [a] H. K. Schnoes, D. W. Thomas, R. Aksornvitaya, W. R. Schleigh, and S. M. Kupchan, *J. Org. Chem.*, 1968, **33**, 1225; [b] C. Hootele, R. Levy, M. Kaisin, J. Pecher, and R. H. Martin, *Bull. Soc. chim. belges*, 1967, **76**, 300; [c] B. Hwang, J. A. Weisbach, B. Douglas, R. Raffauf, M. P. Cava, and K. Bessho, *J. Org. Chem.*, 1969, **34**, 412; [d] D. W. Thomas and K. Biemann, *Tetrahedron*, 1968, **24**, 4223.

[84] M. P. Cava, Y. Watanabe, K. Bessho, J. A. Weisbach, and B. Douglas, *J. Org. Chem.*, 1968, **33**, 3350.

[85] R. L. Augustine and W. G. Pierson, *J. Org. Chem.*, 1969, **34**, 1070.

[86] S. I. Sallay, *J. Amer. Chem. Soc.*, 1967, **89**, 6762.

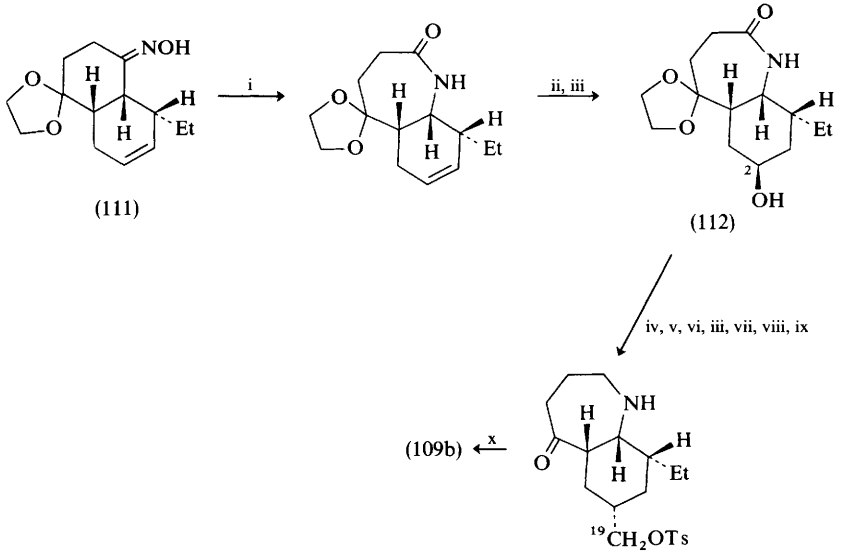
[87] [a] W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *J. Amer. Chem. Soc.*, 1968, **90**, 1650; [b] S. Hirai, K. Kawata, and W. Nagata, *Chem. Comm.*, 1968, 1016.



Scheme 18

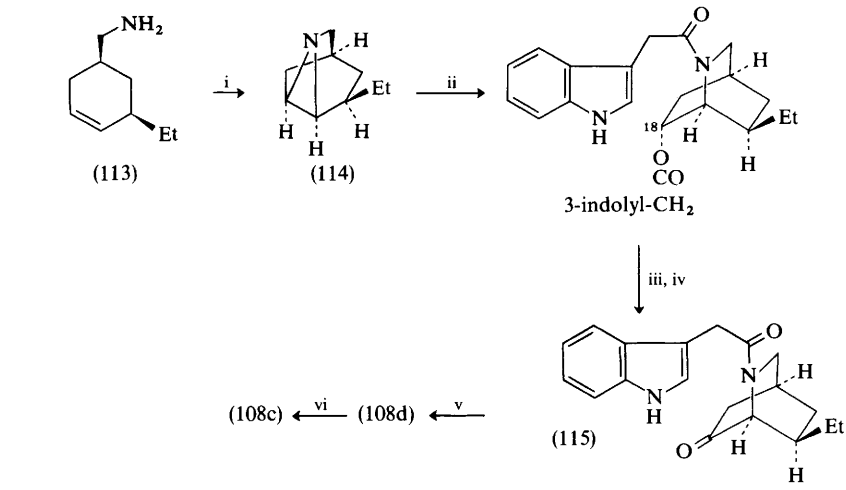
Reagents: i, $AcCl–AlCl_3$; ii, H_2–Pd/C; iii, $LiAlH_4$; iv, Ac_2O; v, $KMnO_4$; vi, Br_2–NaOH; vii, NaOH; viii, H_2–Ru/C–100 °C and 2000 p.s.i.g.; ix, CrO_3; x, $PhNHNH_2$; xi, PPA.

aziridine (114). This not only contained the desired isoquinuclidine system, but also, by treatment with 3-indolylacetic anhydride, allowed simultaneous introduction of the tryptamine unit *and* the insertion of an oxygen function at C(18), which was used later in the cyclisation [(115) → (108d)] on to the indole α-position.



Scheme 19

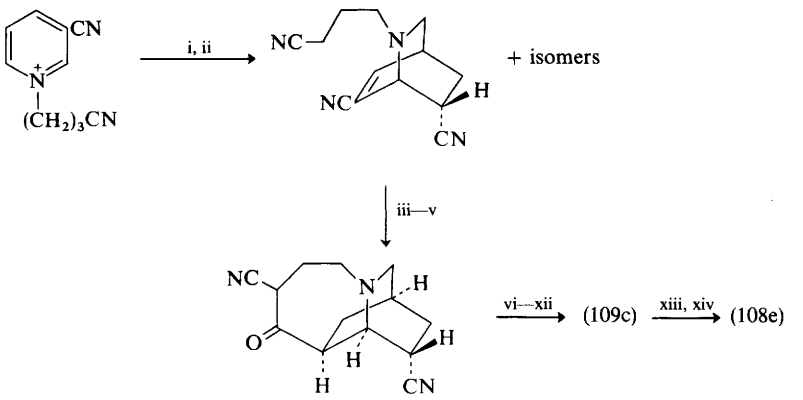
Reagents: i, TsCl–pyridine; ii, $PhCO_3H$; iii, $LiAlH_4$; iv, CrO_3–pyridine; v, $Ph_3P{:}CH_2$; vi, B_2H_6; vii, $PhCH_2O{\cdot}COCl$; viii, TsCl; ix, AcOH–HBr; x, $Me_2CH(CH_2)_2OH$–heat.



Scheme 20

Reagents: i, $Pb(OAc)_4$; ii, $(3\text{-indolyl-}CH_2CO)_2O$; iii, NaOH; iv, Ac_2O–DMSO; v, TsOH; vi, AlH_3.

A second group of Japanese workers have synthesised (±)-ibogamine[88b] and (±)-epi-ibogamine[88a] (108e) (Scheme 21). Their method of making the isoquinuclidine moiety was similar to that used in Büchi's pioneering synthesis, but in this case all the aliphatic portion (109c) of the molecule was made first and then subjected to Fischer indole cyclisation. The seven-membered heterocyclic ring was produced by a Ziegler cyclisation.



Scheme 21

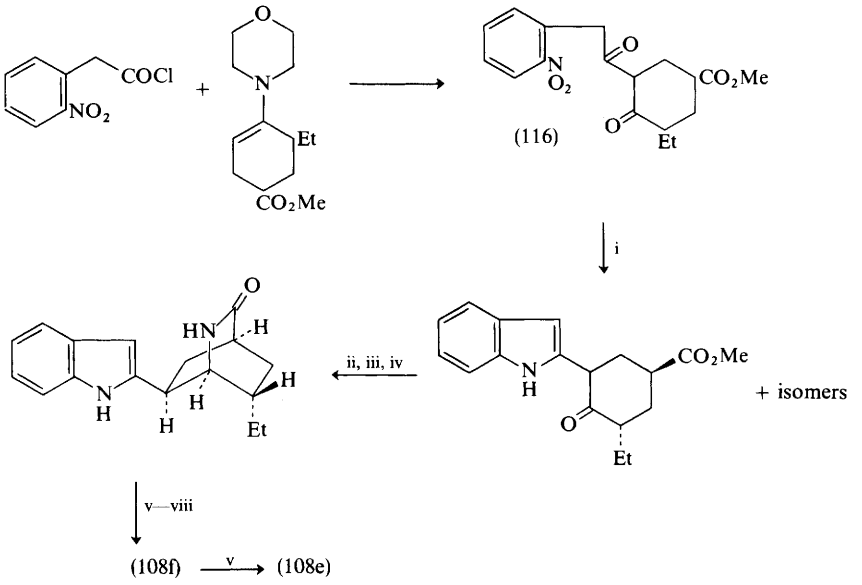
Reagents: i, $NaBH_4$–Na_2CO_3; ii, CH_2:CHCN; iii, H_2–Pt; iv, PhNMeLi; v, AcOH; vi, c·HCl–heat; vii, CH_2N_2; viii, $(CH_2OH)_2$–TsOH; ix, $MeSOCH_2Na$; x, Al–Hg; xi, N_2H_4–KOH; xii, 10% HCl; xiii, $PhNHNH_2$; xiv, HCO_2H.

A different route[89] has given (±)-epi-ibogamine (Scheme 22). Here the indole nucleus was synthesised by the hydrogenation of the diketone (116). This α-substituted indole was then transformed into a 2-indolylisoquinuclidine (117) and the final ring closure, after attachment of the two-carbon chain to the aliphatic nitrogen, made at the indole β-position; this is the only iboga synthesis announced so far to do this.

Büchi has modified[90] his original approach to produce (±)-velbanamine (118) (Scheme 23) and catharanthine. The isoquinuclidine intermediate (119) was degraded to (120). Linking to the indole was followed by a cleavage (121) → (122) made possible by the 3-hydroxy-ketone unit, and the intermediate (122) elaborated into velbanamine.

Secodine Group. In the biogenetic interrelationship of the three major monoterpene-tryptamine alkaloid types, *i.e.* strychnos, aspidosperma, and iboga, the necessary changes in the aliphatic skeleton can be schematically represented

[88] [a] Y. Ban, T. Wakamatsu, Y. Fujimoto, and T. Oishi, *Tetrahedron Letters*, 1968, 3383; [b] M. Ikezaki, T. Wakamatsu, and Y. Ban, *Chem. Comm.*, 1969, 88.
[89] P. Rosenmund, W. H. Haase, and J. Bauer, *Tetrahedron Letters*, 1969, 4121.
[90] G. Büchi, P. Kulsa, and R. L. Rosati, *J. Amer. Chem. Soc.*, 1970, **92**, 999.



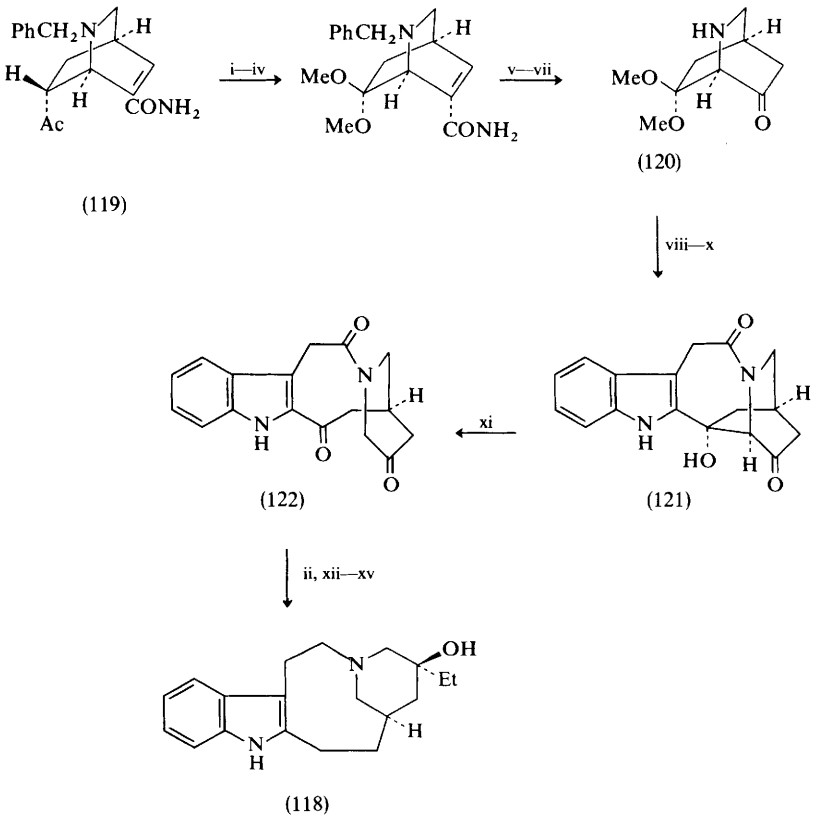
Scheme 22

Reagents: i, H_2–Pd/C; ii, H_2NOH; iii, H_2–Ni; iv, heat; v, $LiAlH_4$; vi, $BrCH_2CO_2Me$; vii, NaOH; viii, PPA.

(123) by one of two processes, *viz.* cleavage at *x* followed by reattachment either at *a* (→ aspidosperma) or at *b* and *c* (→ iboga). It was thus of the utmost significance when recently[91–94] compounds in which only the cleavage *x* had occurred were isolated or recognised as natural products. The alkaloids which fall into this category may well result from an irreversible trapping of an intermediate from the interconversion pathway.

It is known that the biological interconversions take place at an alkaloidal level and speculation has centred on a species (132) (Scheme 26 and also Chapter 2) as the key to the process, in which the three-carbon fragment resulting from cleavage *x* is attached to the indole α-position. The base (124) from *Tabernaemontana cumminsii*,[91] the structure of which was verified by synthesis, is clearly of the type (132), although one carbon of the three-carbon indole α-substituent has been lost.

[91] P. A. Crooks, B. Robinson, and G. F. Smith, *Chem. Comm.*, 1968, 1210.
[92] [a] G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Comm.*, 1970, 189; [b] R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *ibid.*, p. 190; [c] A. R. Battersby and A. K. Bhatnagar, *ibid.*, p. 193.
[93] G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Comm.*, 1970, 191.
[94] D. A. Evans, G. F. Smith, G. N. Smith, and K. S. J. Stapleford, *Chem. Comm.*, 1968, 859.



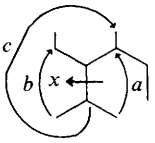
Scheme 23

Reagents: i, O_2–Bu^{t}OK; ii, $NaBH_4$; iii, $NaIO_4$; iv, $(MeO)_3CH$–MeOH–TsOH; v, NaOCl; vi, Na_2CO_3–H_2O; vii, H_2–Pd/C; viii, 3-indolyl-CH_2CO_2Na–EtN:C:$N(CH_2)_3NMe_2$; ix, TsOH; x, AcOH–$HClO_4$; xi, Bu^{t}OK; xii, Sn–$SnCl_2$–AcOH–TsOH; xiii, $C_6H_{11}N$:C:NC_6H_{11}–DMSO–H^+; xiv, EtMgBr; xv, $LiAlH_4$.

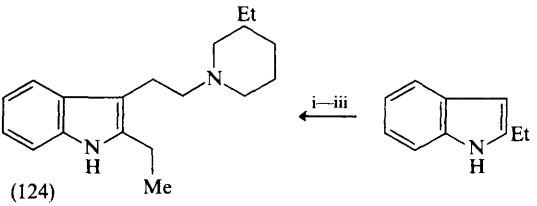
Even closer to the postulated biogenetic intermediate are the structures of a group of alkaloids isolated from *Rhazya stricta* and/or *R. orientalis.* These are four monomers,[92] derivatives of secodine (SD) (125a), and two dimeric groups, one based on presecamine[93] (126) and the other on secamine[94] (127).*

The structures of 15,16,17,20-tetrahydrosecodine (125b) and 16,17-dihydrosecodine (129) were assigned[92a] on the basis of their spectra. Mass spectroscopy

* These dimeric alkaloids are discussed in detail in the following chapter.



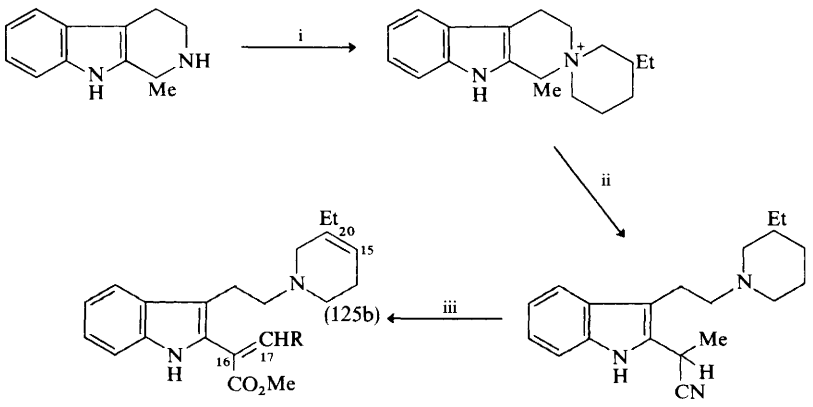
(123)



(124)

Reagents: 1, $(COCl)_2$; ii, 3-ethylpiperidine; iii, $LiAlH_4$.

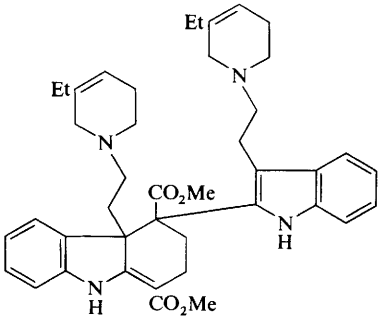
is helpful for monomers and dimers in this group of alkaloids: they show dominant fragment ions at *m/e* 124 (128) or 126 (128a), according to whether the piperidine ring(s) carries a double bond or is fully saturated. Both bases have been synthesised; Scheme 24 shows the route to (±)-(125b).



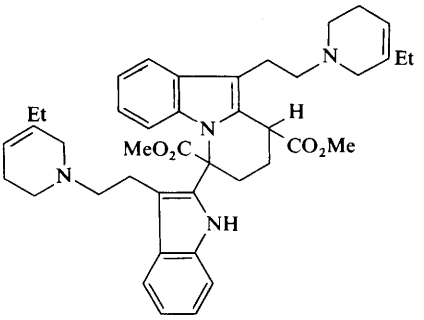
(125)a; H
b; H, 15,16,17,20-tetrahydro
(129); H, 16,17-dihydro
(130); OH, 16,17-dihydro
(131); OH, 15,16,17,20-tetrahydro

Scheme 24

Reagents: i, $I(CH_2)_3CHEtCH_2I$; ii, KCN; iii, $MeOH–H^+$.

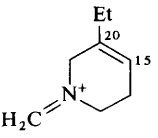


(126)



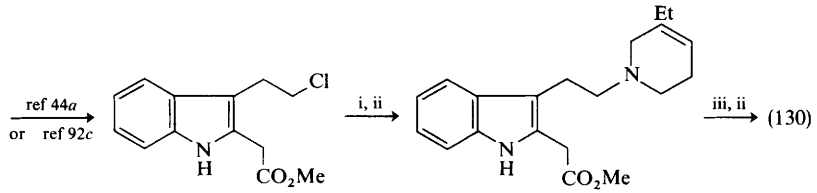
(127)

The naturally occurring alcohols, 16,17-dihydrosecodine-17-ol (130) and 15,16,17,20-tetrahydrosecodine-17-ol (131) have also been synthesised[92a,c]; Scheme 25 illustrates the synthesis of (±)-(130) which confirmed the position of the double bond in the piperidine ring.



(128)

a; 15,20-dihydro



Scheme 25

Reagents: i, 3-ethylpyridine; ii, $NaBH_4$; iii, HCO_2Me–tritylsodium.

Rearrangements of Iboga *and* Aspidosperma *Types.* It is possible to envisage the biological rearrangements of the monoterpene-tryptamine alkaloid skeleta as proceeding *via* a common intermediate (132), reversibly derivable, at least on paper (see below) from each of the skeletal types, providing that a structure at the correct oxidation level is chosen. Thus tabersonine (133) (aspidosperma),

catharanthine (134) (iboga), and an isomer (135) plausibly derivable from stemmadenine (65) (strychnos) are suitable representatives of the three types. Based on the possibility that these compounds might rearrange *via* (132) or a related species, *in vitro* attempts[95] have been made to effect such interchanges. Unfortunately earlier claims[95a,b] that, when heated in acetic acid, stemmadenine (65) is converted into tabersonine (133) and that this in turn is converted into catharanthine (134), which seemed so nicely to provide the desired *in vitro* analogy, have not been substantiated by subsequent work.[95d] However, both tabersonine and catharanthine do undergo rearrangements[95c,d] and degradations in proton-catalysed[95c] or thermal treatments,[95c,d] and at least some of these seem best rationalised by assuming the intermediacy of (132). Scheme 26 summarises the results obtained with tabersonine, catharanthine, and ψ-catharanthine (136).

Tabersonine (133), when heated in acetic acid, gave[95d] *allo*-catharanthine (137), dihydro-*allo*-catharanthine, acetoxydihydro-*allo*-catharanthine (138), and vincadifformine (139). The rearrangement can be visualised as proceeding by isomerisation of an intermediate (141) (Scheme 27) and reclosure (142). Stemmadenine heated with acetic acid gave stemmadenine *O*-acetate.

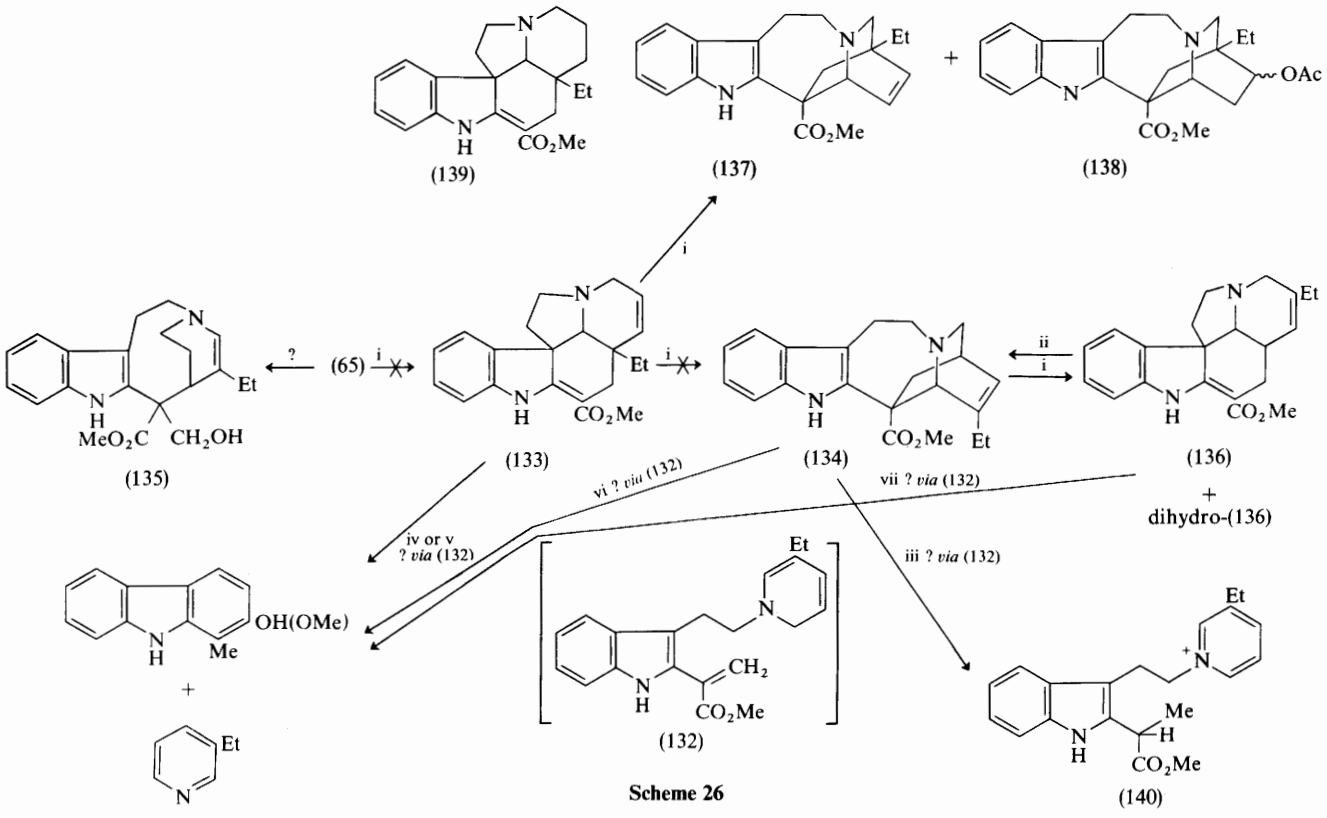
Tabersonine heated alone[95d] or in xylene[95c] and catharanthine and ψ-catharanthine heated in xylene[95c] gave 2-hydroxy-1-methylcarbazole,[95c,d] 2-methoxy-1-methylcarbazole,[95c,d] and 3-ethylpyridine.[95c] These products are considered to arise *via* (132); the closure of the carbazole C ring and the expulsion of 3-ethylpyridine are closely analogous to processes which led to 2-hydroxycarbazole and 3-ethylpyridine when akuammicine was decomposed in hot methanol.[95e] When catharanthine was heated in methanol[95c] the salt (140) was formed, again, it is thought, *via* (132), the methanol promoting an intramolecular oxidation–reduction which diverted the decomposition from the path it took in an aprotic solvent.

The formation of the key species (132) from (133), (134), or (135) can be viewed either as an ionic process [*e.g.* from (133), *via* (141), as shown in Scheme 27] or from (133) and (134) as an electrocyclic process which would lead to (132) directly [*e.g.* from aspidosperma system, dotted arrows in (133), in Scheme 27]. It is considered[95c] that both types of mechanism may operate, according to the precise reaction conditions.

The loss of acetaldehyde from voacristine (143) when it was heated in acetic acid[96] may well proceed by way of (144), produced by a reverse Mannich reaction (*cf.* Scheme 28); note that (144) is an intermediate of the type necessary for the conversion of an iboga type into (132) by an ionic route. 4,20-Dehydrovoacangine (145) was also produced in this reaction.

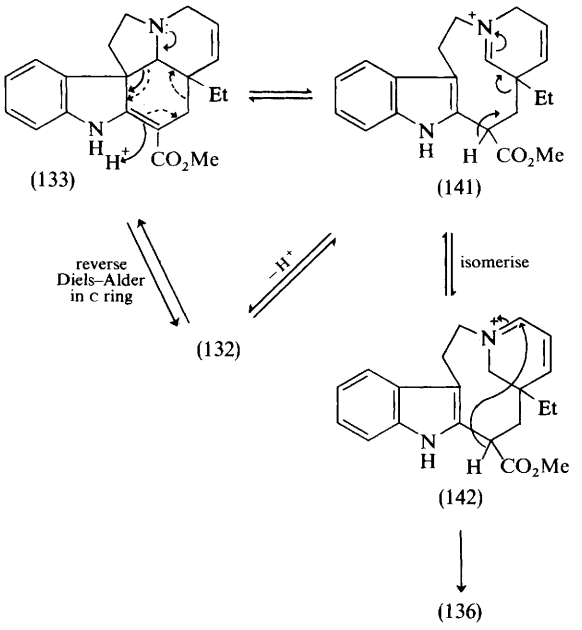
[95] [a] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 945; [b] A. A. Qureshi and A. I. Scott, *ibid.*, 1968, 947; [c] A. I. Scott and P. C. Cherry, *J. Amer. Chem. Soc.*, 1969, **91**, 5872; [d] R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, *Chem. Comm.*, 1969, 1475; [e] P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 1961, 1458.

[96] A. Goldblatt, C. Hootele, and J. Pecher, *Chimia* (*Switz.*), 1969, **23**, 400.

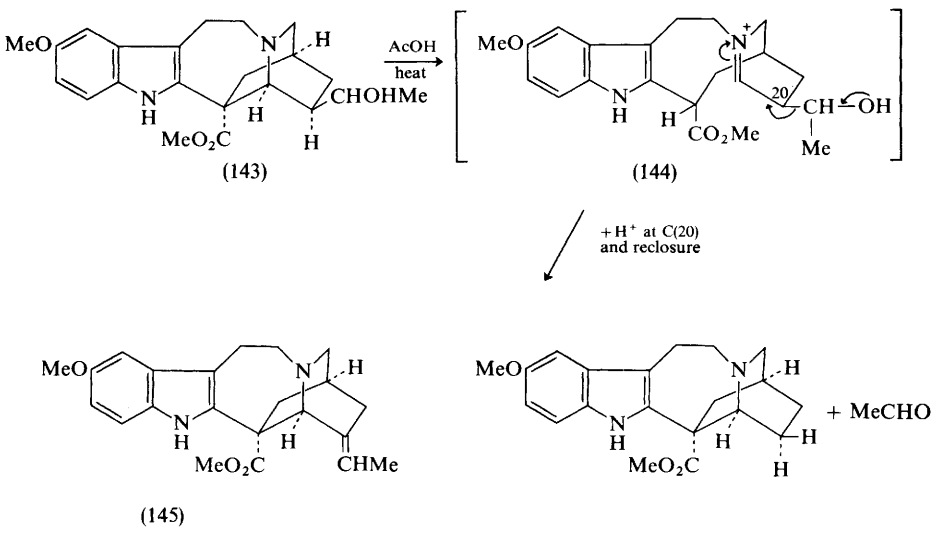


Scheme 26

Reagents: i, AcOH–heat; ii, AcOH–heat, reverse reaction proceeds to no more than 1%; iii, MeOH–140 °C; iv, xylene–205 °C; v, 190 °C; vi, xylene–140 °C; vii, xylene–175 °C.



Scheme 27



Scheme 28

3 Biogenetically Related Quinoline Alkaloids

Full details[97a] have been published of the structural work[1g] on the *Melodinus* alkaloids.

The mass spectra of partially reduced cinchonines have been examined.[97b] In comparing the n.m.r. spectra of the racemic and optically active forms of dihydroquinine, measured in an achiral solvent ($CDCl_3$), it was observed[98] that significant differences (up to 0.2 τ) existed between the resonance positions of corresponding hydrogen atoms, especially those attached to the aromatic nucleus. This phenomenon, which clearly makes it necessary to exercise care in using n.m.r. comparison for the identification of natural with synthetic racemic materials, is due to differing solute–solute interactions in solutions containing pure enantiomers compared with racemic mixtures. The phenomenon was less marked in dilute solution or for the corresponding acetates.

Hydrogenolysis of the *C*(9)-hydroxy-group of typical *Cinchona* quinoline alkaloids, as well as reduction of the B ring, occurs on sodium–amyl alcohol treatment.[99a] Irradiation[99b] in acid solution causes hydrogenolysis of the *C*(9)-hydroxy-group, *e.g.* quinine affords 9-deoxyquinine.

New synthetic approaches[100] to the quinine system have a common quinuclidine-forming process. This involves the intramolecular addition of a secondary amine function to a vinylquinoline, for example (147) → (146c), *via* (147a). Scheme 29 sets out the nine-step synthesis[100a] of quinine (146a) and quinidine (146b), starting from *N*-benzoylhexahydroisoquinolone (148).

10-Hydroxy- (149a) and 10-methoxy-camptothecin (149b) have been isolated[101a] from *Camptotheca acuminata* from which the parent alkaloid (149c) was earlier obtained.[101b] So far only model compounds have been obtained[102] in a search for a method for synthesising this fascinating molecule, which almost certainly is biogenetically related[102a,103] to the indole alkaloids of a type closely similar to vallesiachotamine. Three groups have succeeded in producing compounds containing rings A, B, and C of the alkaloid. Thus pentacyclic

[97] [a] W. E. Oberhänsli, *Helv. Chim. Acta*, 1969, **52**, 1905; K. Bernauer, G. Englert, W. Vetter, and E. Weiss, *ibid.*, p. 1886; [b] B. Golankiewicz, *Bull. Acad. polon. Sci., Sér. Sci. chim.*, 1969, **17**, 655 (*Chem. Abs.*, 1970, **72**, 133042y).

[98] T. Williams, R. G. Pitcher, P. Bommer, J. Gutzwiller, and M. Uskoković, *J. Amer. Chem. Soc.*, 1969, **91**, 1871.

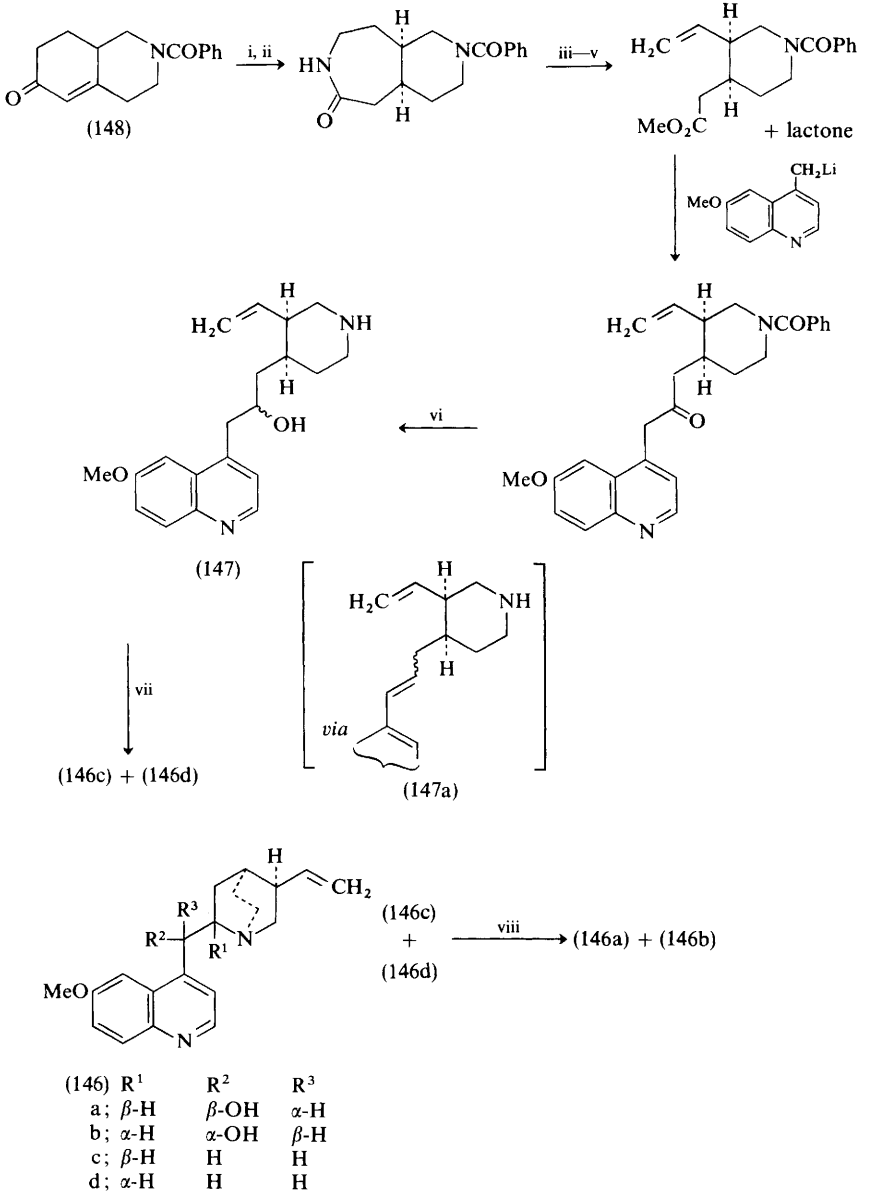
[99] [a] J. Suszko and B. Golankiewicz, *Roczniki Chem.*, 1968, **42**, 637 (*Chem. Abs.*, 1969, **71**, 50289n); [b] V. I. Sternberg, E. F. Travecedo, and W. E. Musa, *Tetrahedron Letters*, 1969, 2031.

[100] [a] M. Uskoković, J. Gutzwiller, and T. Henderson, *J. Amer. Chem. Soc.*, 1970, **92**, 203; J. Gutzwiller and M. Uskoković, *ibid.*, p. 204; [b] M. Gates, B. Sugavanam, and W. L. Schreiber, *ibid.*, p. 205.

[101] [a] M. C. Wani and M. E. Wall, *J. Org. Chem.*, 1969, **34**, 1364; [b] M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, 1966, **88**, 3888.

[102] [a] E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Amer. Chem. Soc.*, 1967, **89**, 6741; [b] M. Shamma and L. Novak, *Tetrahedron*, 1969, **25**, 2275; [c] J. A. Kepler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, 1969, **34**, 3853; [d] M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Comm.*, 1970, 404.

[103] M. Shamma, *Experientia*, 1968, **24**, 107.

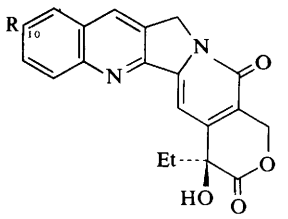


(146) R^1 R^2 R^3

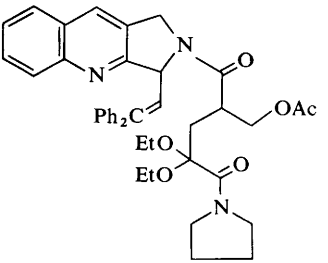
a; β-H β-OH α-H
b; α-H α-OH β-H
c; β-H H H
d; α-H H H

Scheme 29

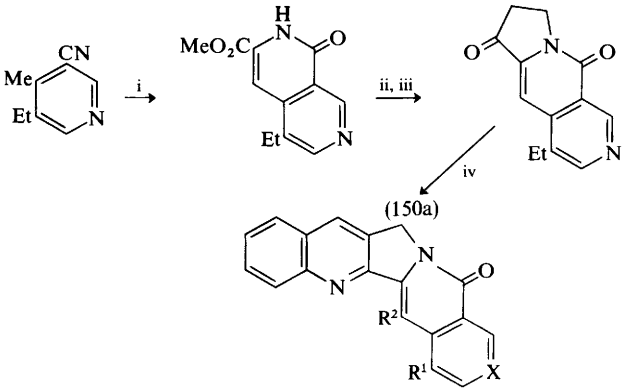
Reagents: i, NaN_3–H_2SO_4; ii, H_2–Rh/Al_2O_3; iii, N_2O_4; iv, 125 °C; v, esterify; vi, $(Bu^i)_2AlH$/–78 °C; vii, AcOH–heat; viii, O_2–Bu^tOK–DMSO–Bu^tOH.



(149) R
a; OH
b; OMe
c; H



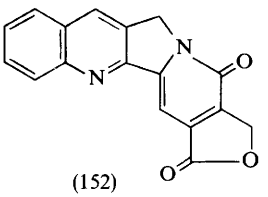
(151)



(150) R¹ R² X
a; Et H N
b; H H CH
c; H OH CH
d; H OH N

Scheme 30

Reagents: i, $(MeO_2C)_2$–Bu^{t}OK; ii, CH_2:$CHCO_2Me$–Na_2CO_3–DMF; iii, HCl–heat; iv, NaOH–2-aminobenzaldehyde.



(152)

analogues (150a),[102a] (150b),[102b] (150c),[102b] and (150d)[102b] of camptothecin and the potential precursors (151)[102c] and (152)[102d] have been prepared, though difficulties were encountered in attempts to elaborate (151). Scheme 30 shows the route[102a] which was used to synthesise (150a).

14

Bisindole Alkaloids

BY A. A. GORMAN, M. HESSE, AND H. SCHMID; PHARMACOLOGY SECTION BY P. G. WASER AND W. H. HOPFF

One of the newer groups of indole alkaloids is that of the bisindole alkaloids or 'dimeric' indole alkaloids as they are commonly called, although in only very few instances is the term 'dimeric' strictly applicable. Under the heading 'Bisindole Alkaloids' we include those natural products which are clearly comprised of two individual units which in the strict sense would be classed as indole alkaloids* in their own right. More than eighty such products have been reported to date, but although a number have been known for many years, actual structural elucidation goes back only twelve years. This fact clearly demonstrates that without the recent rapid development of separation and analytical techniques this particular field would have remained virtually unopened.

On the basis of structure the 'dimers' can be clearly divided into two groups. The first is comprised of alkaloids with identical or very closely related components in which the same centres act as linkage positions. The Calycanthaceous and Calabash-curare–South American *Strychnos* alkaloids make up this group. The second group consists of 'dimeric' bases in which the alkaloid components are of a different structural type (*e.g.* geissospermine, vinblastine, and tubulosine) or in which two similar 'halves' are linked unsymmetrically through two different centres (*e.g.* macralstonine). The bisindole alkaloids will be discussed in this order.†

Such compounds often exhibit chemical and spectral behaviour which is specifically characteristic of the 'dimeric' structure. Also of paramount interest are the specific pharmacological properties of certain of these alkaloids, such as the muscle relaxation action of the curare alkaloids and the anti-leukemia activity of the *Vinca* alkaloids leurocristine and vinblastine. Such aspects will be discussed in the last two sections of the review.

[1] M. Hesse, Indolalkaloide in Tabellen, Berlin, Göttingen, Heidelberg: Springer-Verlag, 1964, Ergänzungswerk 1968.

* Under indole alkaloids we include naturally occurring bases or their derivatives which contain a true indole nucleus or a modification thereof, indoline (dihydroindole), *N*-acyl-indoline, indolenine, oxindole *etc.*

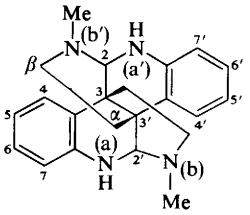
† As a general rule physical data will not be given. They are summarised in the catalogue 'Indolalkaloide in Tabellen.'[1]

1 Calycanthaceous Alkaloids*

This group totals eight alkaloids, namely the 'dimers' calycanthine [$(C_{11}H_{13}N_2)_2$] and its isomers chimonanthine and *meso*-chimonanthine, calycanthidine ($C_{11}H_{13}N_2 \cdot C_{12}H_{15}N_2$) and folicanthine [$(C_{12}H_{15}N_2)_2$], the 'trimer' hodgkinsine ($C_{11}H_{13}N_2 \cdot C_{11}H_{12}N_2 \cdot C_{11}H_{13}N_2$) and the isomeric 'tetramers,' the quadrigemines A and B ($C_{11}H_{13}N_2 \cdot C_{11}H_{12}N_2 \cdot C_{11}H_{12}N_2 \cdot C_{11}H_{13}N_2$).† These alkaloids are unique in that their biosynthesis apparently involves the oxidative coupling of two indole nuclei at the β-position.

Since the first five alkaloids mentioned have been discussed in a recent review[2] they will only be briefly described here, the emphasis being placed on more recent aspects.

Calycanthine (1).—The alkaloid occurs in both genera of Calycanthaceae, namely *Calycanthus* L. and *Chimonanthus* Lindl. (*Meratia* Loisel.). Although this base does not possess an indole skeleton, the elucidation of its structure and in particular Robinson's biogenetic proposals which ultimately led to its structure, were of such importance with respect to the rest of this group that its inclusion here is a necessity. The structural work on calycanthine began at a time when



(1), Calycanthine

modern spectroscopic methods were still in their infancy. From the observation that calycanthine gave a pink colour reaction with Ehrlich's reagent it was concluded that the alkaloid was an indole derivative. The isolation of indoles from oxidation and pyrolysis reactions could only support this assumption. The most important of the pyrolysis products was calycanine (2) whose structure was proved by synthesis. On the basis of this structure, Robinson[3] came to the conclusion that calycanthine was formed in nature *via* oxidative coupling of two $N_{(b)}$-methyltryptamine units. The bisindolenine (3) thus formed is equivalent to the tetra-amino-dialdehyde (4). Although the structure (5) derived for calycanthine from consideration of (3) and (4) turned out to be wrong, (4) is certainly

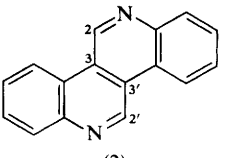
[2] R. H. F. Manske, 'The Alkaloids of Calycanthaceae,' 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII. The Indole Alkaloids, Academic Press, New York, 1965, p. 581.

[3] R. Robinson and H. J. Teuber, *Chem. and Ind.*, 1954, 783.

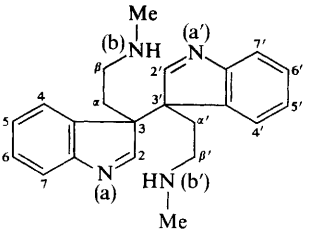
* The numbering corresponds to that accepted for tryptamine.

† Although hodgkinsine and the quadrigemines A and B are not strictly 'dimers' we think that their inclusion here is appropriate.

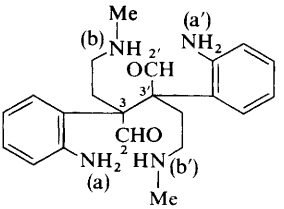
the potential precursor of the alkaloid. Coupling of the nucleophilic and electrophilic centres of (4) in an alternative manner, namely $N_{(a)}$ and $N_{(b)}$ with C(2′) and $N_{(a')}$ and $N_{(b')}$ with C(2) leads to structure (1), which has been proved chemically and by *X*-ray analysis. The stereochemistry shown is absolute.



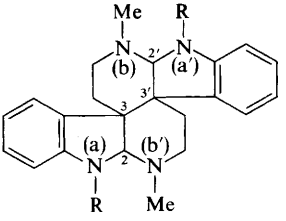
(2)



(3)



(4)



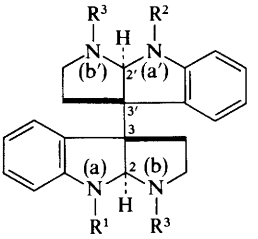
(5) R = H
(14) R = Me

Folicanthine (6), Chimonanthine (7), *meso*-Chimonanthine (8), and Calycanthidine (9).—Folicanthine occurs in *Calycanthus floridus* L. and *C. occidentalis* Hook. et Arn. It follows from molecular weight determinations and the isolation of 1.6 moles of $N_{(a)}N_{(b)}$-dimethyl-2,3-dihydrotryptamine (10) on zinc–acid reduction that it is a dimer of $N_{(a)}N_{(b)}$-dimethyltryptamine. Treatment of folicanthine dimethiodide with sodium hydroxide gives the key compound (11), whose structure follows from its ready acid-catalysed cleavage to the indole (12) and the oxindole (13).

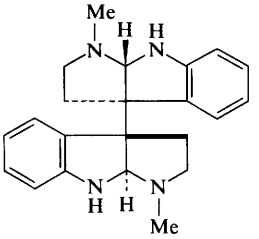
These results, and consideration of Robinson's biogenetic scheme, lead to the alternative structures (6) or (14) for folicanthine. The ready mass spectral fragmentation of the alkaloid into two equal halves favours structure (6).[4,5]

The alkaloids chimonanthine and calycanthidine are $N_{(a)}N_{(a')}$-bisdesmethylfolicanthine (7) and $N_{(a)}$-desmethylfolicanthine (9) respectively. *N*-Methylation in both cases gives folicanthine (6).[6] An *X*-ray analysis of chimonanthine dihydrobromide has confirmed the structure of this alkaloid as (7) and thus those of folicanthine and calycanthidine as (6) and (9).

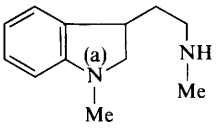
[4] E. Clayton, R. I. Reed, and J. M. Wilson, *Tetrahedron*, 1962, **18**, 1495.
[5] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Elucidation of Natural Products by Mass Spectrometry,' Vol. I, 'Alkaloids,' Holden Day, San Francisco, 1964, p. 167.
[6] W. G. Bardsley, Thesis, University of Manchester, 1963.



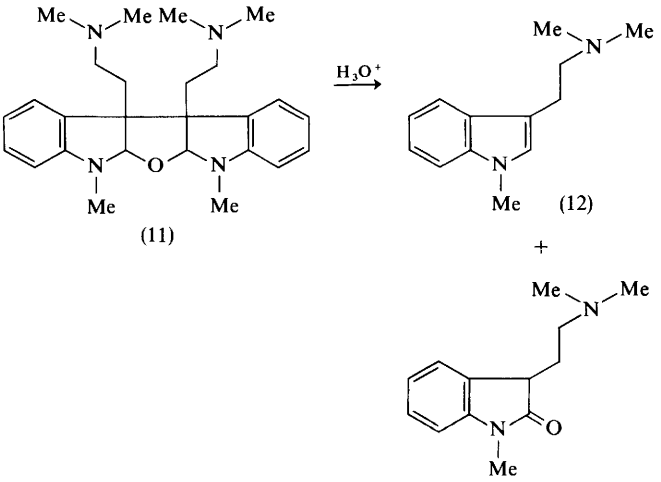
(6) $R^1 = R^2 = R^3 = Me$; Folicanthine
(7) $R^1 = R^2 = H$; $R^3 = Me$; Chimonanthine
(9) $R^1 = H$; $R^2 = R^3 = Me$; Calycanthidine



(8), *meso*-Chimonanthine



(10)



(11)

(12)

+

(13)

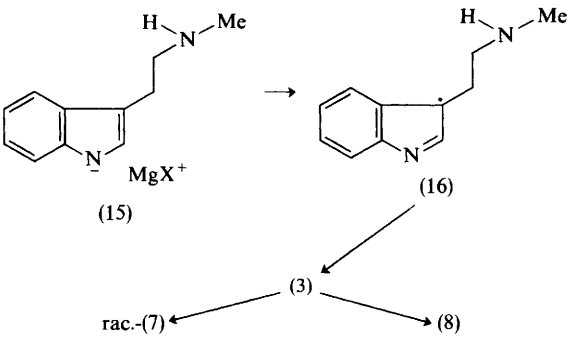
The absolute configuration of the aforementioned alkaloids has been determined from circular dichroism measurements.[7]

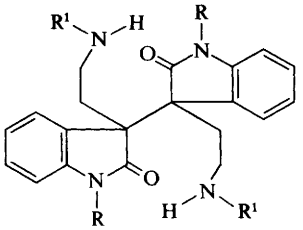
The synthesis of racemic chimonanthine has been realised in two ways. In the first case an ethereal solution of the Grignard derivative of $N_{(b)}$-methyltryptamine (15) is treated with ferric chloride. Hydrolysis gives unchanged (15), racemic chimonanthine [racemic (7)] in 19% yield, and *meso*-chimonanthine (8) in

[7] S. F. Mason and G. W. Vane, *J. Chem. Soc.* (*B*), 1966, 370.

7% yield. The primary reaction product is most probably the indolyl radical (16), two of which react to give racemic (7) and (8). The racemic form, when heated in acetic acid, is converted into a 1 : 4 equilibrium mixture of itself and racemic calycanthine [racemic (1)]. The *meso*-chimonanthine (8) gives the corresponding *meso*-equilibrium mixture. *meso*-Chimonanthine occurs with chimonanthine (7) in *Chimonanthus fragrans* Lindl.[8]

The second synthetic sequence involves bisoxindoles of the type (17). Compound (17) in both racemic and *meso*-forms can be obtained by the action of sodium hydride and iodine on 3-(β-ethoxycarbamidoethyl)oxindole.[9] Reductive cyclisation of racemic (17) with lithium aluminium hydride gives racemic (7) and racemic (1) in low yield; the corresponding *meso*-compound (*meso*-17) gives (8).[9]





(17) R = H; R^1 = COOMe
(18) R = Me; R^1 = H
(19) R = R^1 = Me

The bisoxindole (19) is built up as follows:[10] oxidative coupling of *N*-methyloxindole gives $N_{(a)}N_{(a')}$-dimethyl-3,3′-bisoxindole which can be alkylated, using chloroacetonitrile, at the 3 and 3′ positions. Reduction of the resulting dinitrile

[8] E. S. Hall, F. McCapra, and A. I. Scott, *Tetrahedron*, 1967, **23**, 4131.
[9] J. B. Hendrickson, R. Göschke, and R. Rees, *Tetrahedron*, 1964, **20**, 565.
[10] T. Hino, *Chem. and Pharm. Bull. (Japan)*, 1961, **9**, 979.

gives (18), the double benzaldehyde-Schiff base of which is methylated with methyl iodide and hydrolysed to give (19). Lithium aluminium hydride reduction gives finally racemic folicanthine [racemic (6)].[11]

It has recently been shown that *Calycanthus floridus* plants, on being fed with [2-^{14}C]tryptophan, produce specifically labelled folicanthine (6).[12(cf.13)] Tryptophan is thus serving as a specifically monomeric precursor of folicanthine. It seems highly probable that the biosynthesis also includes the coupling of two indolyl radicals of the type (16).

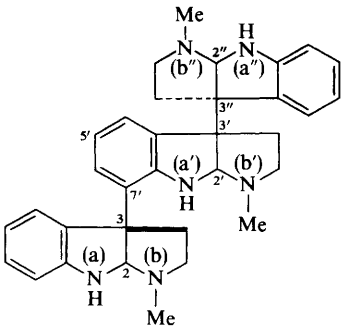
Hodgkinsine (20).—The 'trimeric' optically active hodgkinsine (20; $C_{33}H_{38}N_6$) is found in *Hodgkinsonia frutescens* F. Muell. It was originally concluded to be an isomer of calycanthine (1) but recent investigations have led unambiguously to structure (20) for this alkaloid.[14]

An excess of methyl iodide converts hodgkinsine into the $N_{(b)}N_{(b')}N_{(b'')}$-trimethiodide which with alkali yields the tri-indolenine (21). Sodium borohydride in alkaline ethanolic solution apparently attacks the least hindered 'terminal' imino-functions to give a tetrahydro-derivative (22), which then fragments to yield $N_{(b)}N_{(b)}$-dimethyltryptamine (23) from the top unit and the indole-indoline (24) from the central and lower units. In (24) the two units are linked by means of an aliphatic-aromatic bond, as has been shown by deuterium exchange experiments. Heating of (24) in 8N-D_2SO_4–D_2O gives, after exchange of *N*-bound deuteriums, a hexadeuterio-(24). The indole double bond of (24) can be reduced with zinc and acid to give a di-indoline (25) which under similar deuteriating conditions only gives a trideuterio-(25). When boiled with strong acid (25) is cleaved to give $N_{(b)}N_{(b)}$-dimethyltryptamine (23) and $N_{(b)}N_{(b)}$-dimethyl-2,3-dihydrotryptamine (26).

Since indolines only exchange hydrogen for deuterium at those positions *ortho* and *para* to the nitrogen, and since the u.v. spectrum of (25) is of a bisindoline with a non-conjugated arrangement of the chromophores, it follows that in (25) a position *ortho* or *para* to an $N_{(a)}$-atom must be attached to an aliphatic carbon of the other component. The formation of (23) and (26) on acid cleavage of (25) eliminates the tryptamine side-chains as possible linkage positions. Further, since compound (21) is a tri-indolenine, carbons 3, 3′, and 3″ cannot carry a hydrogen. C(3) is therefore fully substituted in (25) and only two structures are possible for this product, namely those formed by coupling C(3) with C(5′) or C(7′).

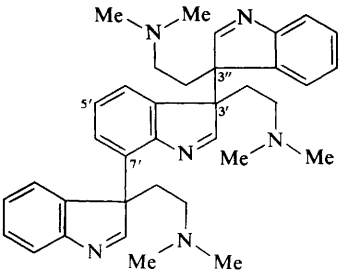
There are two corresponding structures for the indole-indoline (24). In these structures the six exchangeable hydrogens are at positions 2′, 4′, 5′, 6′, 5, and 7 [C(3)–C(7′)-linkage] or 2′, 4′, 6′, 7′, 5, and 7 [C(3)–C(5′)-linkage]. A C(3)–C(5′)-linkage is ruled out as follows: the $N_{(a)}N_{(a')}$-diformyl derivative of (25), on

[11] T. Hino and S. Yamada, *Tetrahedron Letters*, 1963, 1757.
[12] D. G. O'Donovan and M. F. Keogh, *J. Chem. Soc.* (*C*), 1966, 1570.
[13] H. R. Schütte and B. Maier, *Arch. Pharm.*, 1965, **298**, 459.
[14] R. Atitullah, W. G. Bardsley, G. F. Smith, and N. Lahey, 4th Internat. Symp. on Chem. of Natur. Products (IUPAC), Stockholm, June 1966, Abstr. 2B-7: W. G. Bardsley, R. Atitullah, N. Lahey, and G. F. Smith, in preparation.



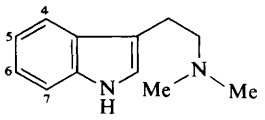
(20), Hodgkinsine

i Me I
ii OH^-



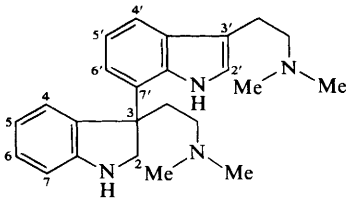
(21)

$NaBH_4$

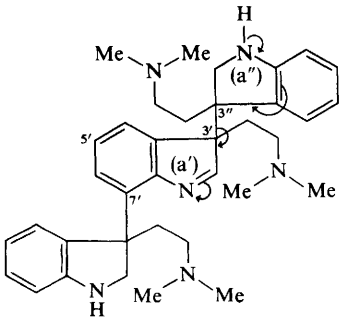


(23)

+



(24)



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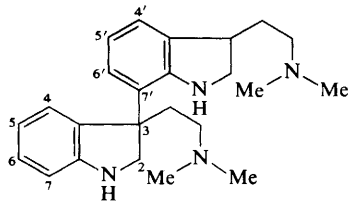
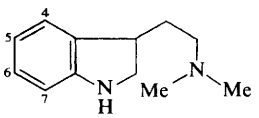


(25)

HCl



(26) + (23)

controlled nitration followed by acid cleavage, yields a mixture of 5-nitro-$N_{(b)}N_{(b)}$-dimethyltryptamine and 5-nitro-$N_{(b)}N_{(b)}$-dimethyl-2,3-dihydrotryptamine. A corresponding 7-nitro-derivative is not formed.

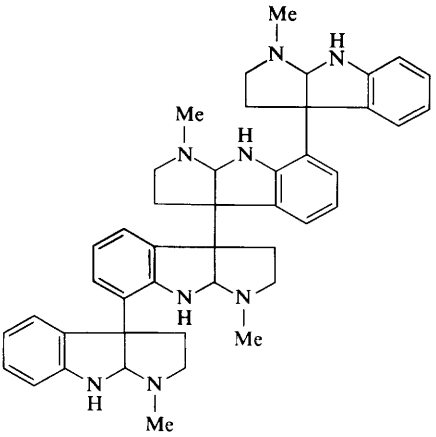
The tri-indolenine (21) and hodgkinsine (20) itself are therefore represented by the structures shown.[14]

The mass spectral behaviour of hodgkinsine is very similar to that of chimonanthine, in that the C(3′)–C(3″) bond is readily broken.[5] This results in the formation of the ions *m/e* 173 and 172 from the top component and ions *m/e* 345 and 344 from the lower two components.

The constitution of hodgkinsine (20) has been confirmed by an *X*-ray analysis of its trimethiodide which also yielded the relative stereochemistry of the alkaloid.[15]

Quadrigemine A (27) and Quadrigemine B (28).[16]—These two isomeric alkaloids ($C_{44}H_{50}N_8$, $M = 690$) occur together with hodgkinsine in *Hodgkinsonia frutescens* F. Muell.

Quadrigemine A (27). In the mass spectrometer the base cleaves into two 'halves', giving only peaks due to fragment ions *m/e* 345 and 344. This indicates the presence of a central chimonanthine-type part. The tetramethiodide of quadrigemine A gives a tetraindolenine, analogous to that from hodgkinsine [(20) → (21)]. Sodium borohydride treatment of this indolenine gives exclusively the indole-indoline (24), identical in all characteristics except rotation with (24) obtained from hodgkinsine. It is possible that the amorphous quadrigemine A is a mixture of stereoisomers.



(27), Quadrigemine A

This degradation leads directly to structure (27) for this 'tetramer'.

Quadrigemine B (28). The alkaloid gives fragment ions *m/e* 172, 173, 516, and 517 in the mass spectrometer. This is strongly indicative of the presence of a chimonanthine-type unit situated at one end of a 'tetrameric' tryptamine derivative.

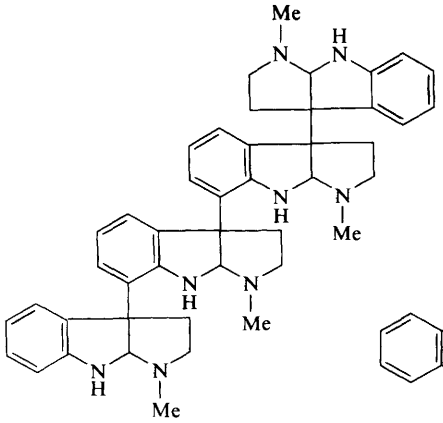
[15] J. Fridrichsons, M. F. Mackay, and A. McL. Mathieson, *Tetrahedron Letters*, 1967, 3521.

[16] K. Parry and G. F. Smith, to be published; K. Parry, Thesis, University of Manchester, 1968.

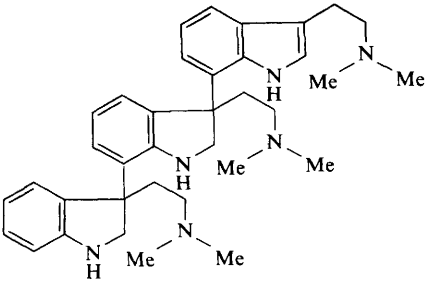
On subjection to the Hofmann degradation procedure quadrigemine B, as expected, forms a tetraindolenine which with sodium borohydride is converted to $N_{(b)}N_{(b)}$-dimethyltryptamine (23) and a 'trimeric' di-indoline-indole (29). Zinc–acid treatment converts (29) into the unstable tri-indoline (30) which, after tri-*N*-formylation, nitration, and hot aqueous mineral acid cleavage, gives a mixture of tars and three products which run on t.l.c. These are 5-nitro-$N_{(b)}N_{(b)}$-dimethyltryptamine, 5-nitro-$N_{(b)}N_{(b)}$-dimethyl-2,3-dihydrotryptamine, and a dinitro-indole-indoline. No 7-nitro- and no unnitrated-tryptamine derivatives are observed. This degradation strongly favours structure (28) for quadrigemine B. This formula is supported by the following observations:

(*a*) The di-indoline-indole (29) exchanges seven carbon-bonded hydrogens for deuterium in D_2SO_4–D_2O.

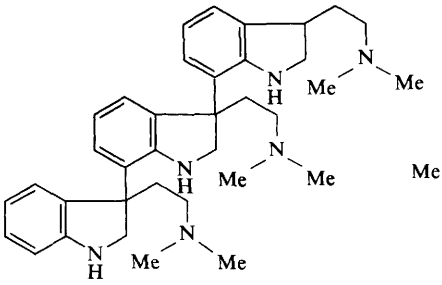
(*b*) Treatment of the tri-indoline (30) with formaldehyde gives an *NN*-methylene derivative. An analogous product is formed from the hodgkinsine degradation product (25). One of the possible alternative structures for the *NN*-methylene compound from (30) is (31). This methylene compound contains



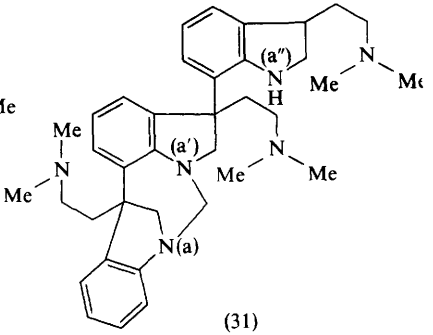
(28), Quadrigemine B



(29)



(30)



(31)

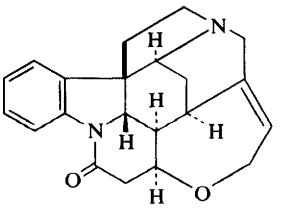
six exchangeable carbon-bonded hydrogens, while that from (25) has five. This observation is readily explained on the basis of (31). The upper and central indoline aromatic rings exchange, as expected, one proton each. The nitrogen atom $N_{(a)}$ of the lower indoline nucleus is at a bridgehead. Its $+M$ effect must therefore, at best, be drastically reduced so that all the protons on the benzene ring become exchangeable. In the alternative formula for the methylene compound the $N_{(a')}$ atom of the central indoline nucleus is at a bridgehead which should again lead to an incorporation of six deuteriums.

2 Alkaloids from Calabash-curare[17–19]

Introduction and Interrelationships.—Calabash-curare is prepared from the bark of South American *Strychnos* of the family Loganiaceae. From the curare and the *Strychnos* species, along with a large number of monomeric indole alkaloids, fifteen structurally classified bisindole alkaloids have been isolated. Their structures are all based on one $C_{38}N_4$ skeleton. Only the $N_{(b)}N_{(b')}$-dimetho-salts exhibit high curare-activity.

All 'dimeric' curare alkaloids are derived from the monomeric units Wieland–Gumlich aldehyde (32) and 18-desoxy-Wieland–Gumlich aldehyde (34) or their respective $N_{(b)}$-metho-salts (33) and (35). The key substance for the synthesis of the 'dimeric' calabash alkaloids is therefore Wieland–Gumlich aldehyde (32). Under the name caracurine VII it has been isolated from the South American *Strychnos toxifera* F. Schomb. and *S. subcordata* Spruce in the form of its $N_{(b)}$-metho-salt (= alkaloid 8 = hemitoxiferine = caracurine VII metho-salt).

The only useful source of Wieland–Gumlich aldehyde is the readily available strychnine (36), obtained from Asiatic sources (*S. nux-vomica* L.). The degradation of strychnine to Wieland–Gumlich aldehyde was first accomplished by



→ → (32)

(36), Strychnine

[17] H. Schmid, Chemie des Calebassencurare, in Curare, Sonderausgabe von Vol. 22/1966, Fasc. 5/6 (S. 391–527) und Vol. 23/1967, Fasc. 1/2 (S. 5–138) des *Bull. Schweiz. Akad. Mediz. Wiss.*; P. Karrer, H. Schmid, and P. Waser, *Farmaco*, 1960, **15**, 126; A. R. Battersby and H. F. Hodson, *Quart. Rev.*, 1960, **14**, 77.

[18] K. Bernauer, *Fortschr. Chem. org. Naturstoffe*, 1959, **17**, 183.

[19] A. R. Battersby and H. F. Hodson, in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII, Academic Press, New York/London, 1965, p. 515.

[20] H. Wieland and K. Kaziro, *Annalen*, 1933, **506**, 60.

H. Wieland[20,21] in 1933. A recent investigation of this degradation has led to a substantial improvement in the efficiency of the process and to a correct formulation of the degradation mechanism.[21a]

When heated in acetic acid–sodium acetate or pivalic acid two molecules of Wieland–Gumlich aldehyde (32) condense in such a way that the two potential aldehyde centres C(17) and C(17′) and the nucleophilic centres $N_{(a)}$ and $N_{(a')}$ form an eight-membered ring, with loss of two molecules of water. One of the possible intermediates (37) on deprotonation gives the most important natural curare alkaloid *C*-toxiferine (38) (= *C*-toxiferine I) (see Scheme 1). This alkaloid contains a bisazacyclo-octadiene ring.

Addition of the two 18- and 18′-hydroxy-groups in (37) leads to caracurine V dimetho-salt (39) which occurs naturally in the ditertiary form. Caracurine V dimetho-salt can be isomerised to *C*-toxiferine (38) by warming with toluene-*p*-sulphonic acid in glacial acetic acid.

The same condensation proceeds between two molecules of $N_{(b)}$-allyl-Wieland–Gumlich aldehyde (40) to give the so-called alloferine (41), which is important clinically.

Under very mild acid catalysis an equilibrium is set up between *C*-toxiferine (38) and caracurine V dimetho-salt (39) and between alloferine (41), tautoferine (42, one ether ring) and the $N_{(b)}N_{(b')}$-diallyl-caracurine V salt (43, two ether rings). These equilibria are strongly dependent on temperature and ionic strength, although in the case of the *N*-allyl compounds the main component is always alloferine (41).[22]

Condensation of Wieland–Gumlich aldehyde (32) itself in acetic or pivalic acid leads predominantly to the tertiary caracurine V (44); bisnor-toxiferine (45) is formed in only small amounts. On heating caracurine V (44) in pure acetic acid under oxygen-free conditions, or its dihydrochloride in distilled water at pH 6.7, bisnor-toxiferine (45) is formed. The latter can be converted back to caracurine V (44) by brief warming with methanolic hydrochloric acid.[23]

C-Dihydrotoxiferine (46, = 18,18′-bisdesoxy-toxiferine) can be prepared as follows: on treatment with hydrogen bromide, caracurine V (44) undergoes ring-opening to give the allylic dibromide (47), which with zinc and acetic acid can be debrominated to the naturally occurring bisnor-dihydrotoxiferine (48). $N_{(b)}N_{(b')}$-Dimethylation gives *C*-dihydrotoxiferine (46).

Acid-catalysed hydrolysis of *C*-dihydrotoxiferine under oxygen-free conditions gives 18-desoxy-Wieland–Gumlich aldehyde metho-salt (35) (hemi-dihydrotoxiferine), which on warming in dilute acetic acid condenses back to *C*-dihydrotoxiferine (46).

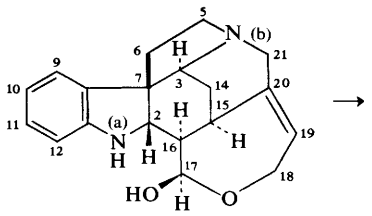
C-Alkaloid H (49), which stands structurally between *C*-dihydrotoxiferine (46) and *C*-toxiferine (38), can be synthesised *via* a mixed condensation involving

[21] H. Wieland and W. Gumlich, *Annalen*, 1932, **494**, 191; G. F. Smith, in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII, Academic Press, New York/London, 1965, p. 592; P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 1961, 1952.

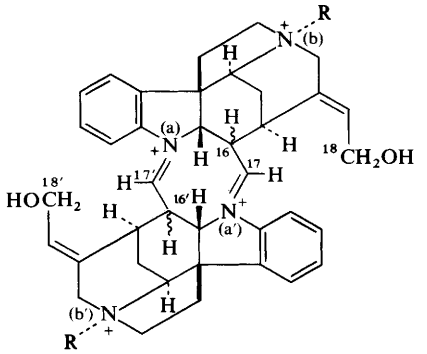
[21a] J. R. Hymon, H. Schmid, P. Karrer, A. Boller, H. Els, P. Fahrni, and A. Fürst, *Helv. Chim. Acta*, 1969, **52**, 1564.

[22] A. Fürst, A. Boller, and H. Els, unpublished; see also ref. 17, p. 11.

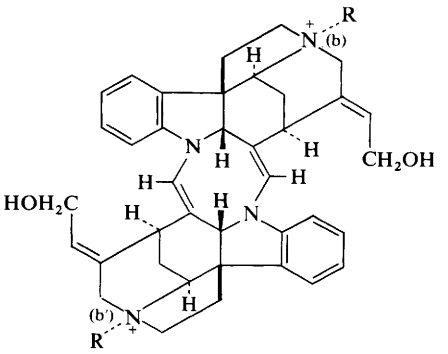
[23] H. A. Hiltebrand, Dissertation, Universität Zürich 1964.



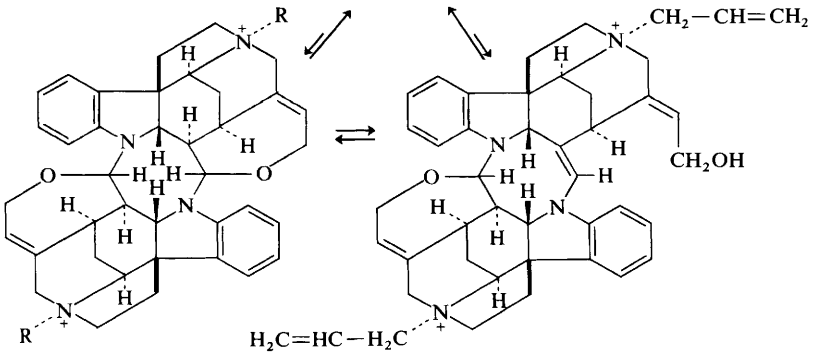
(32) Wieland–Gumlich aldehyde
(33) $\overset{+}{\geqslant}N(b)-Me$
(40) $\overset{+}{\geqslant}N(b)-CH_2-CH=CH_2$



(37)



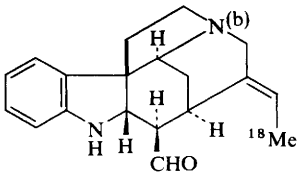
(38) R = Me; *C*-Toxiferine
(41) R = $CH_2-CH=CH_2$; Alloferine
(45) $\geqslant N(b)$, $\geqslant N(b')$; Bisnor-toxiferine



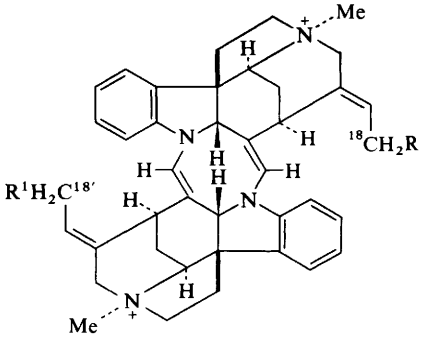
(39) R = Me
(43) R = $CH_2-CH=CH_2$
(44) $\geqslant N(b)$; $\geqslant N(b')$; Caracurine V

(42), Tautoferine

Scheme 1



(34) 18-Desoxy-Wieland–Gumlich aldehyde
(35) $\geqslant \overset{+}{N}$(b)—Me; Hemi-dihydrotoxiferine



(46) R = R^1 = H; *C*-Dihydrotoxiferine
(49) R = H; R^1 = OH; *C*-Alkaloid H
(47) $\geqslant$N(b); $\geqslant$N(b'); R = R^1 = Br
(48) $\geqslant$N(b); $\geqslant$N(b'); R = R^1 = H; *C*-Bisnor-dihydrotoxiferine

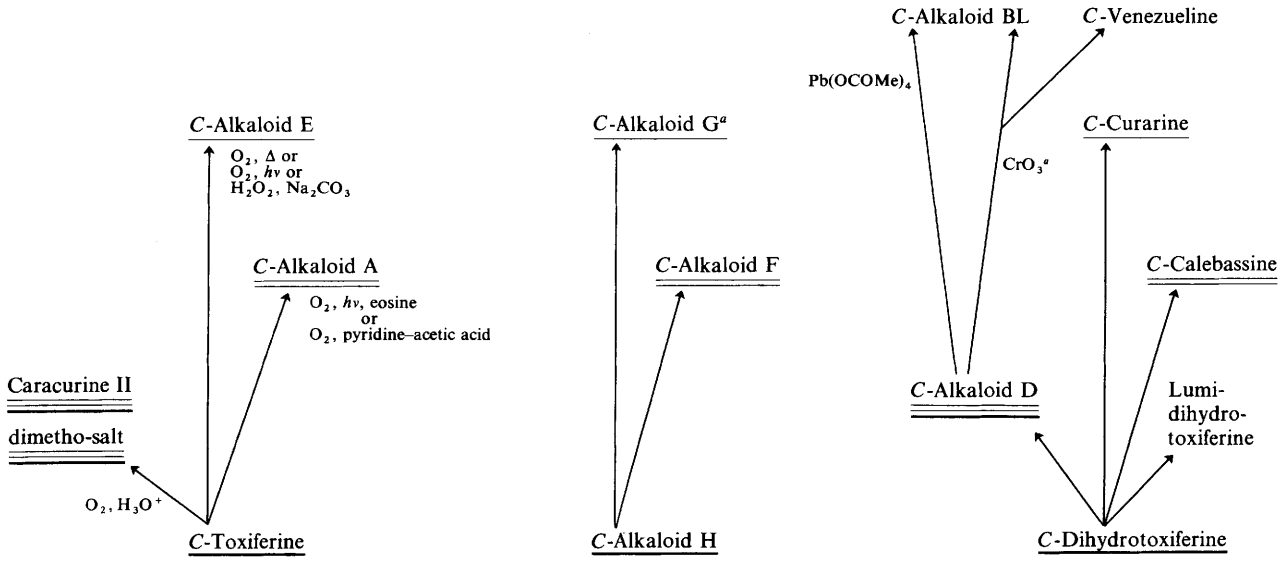
Wieland–Gumlich aldehyde metho-salt (33) and 18-desoxy-Wieland–Gumlich aldehyde (34) followed by $N_{(b)}$-methylation.

The names of *C*-toxiferine (38), *C*-alkaloid H (49), and *C*-dihydrotoxiferine (46) have been assigned to the three distinct families of curare alkaloids, of which each of these is the major representative (see Chart). The individual diquaternary members of these families differ only in the oxidation level of the central diazacyclo-octane ring. Thus, various oxidation processes result in the conversion of *C*-toxiferine (38) to caracurine II dimetho-salt (50), *C*-alkaloid E (51), and *C*-alkaloid A (52). The partial structures of these alkaloids are given in Scheme 2.

C-Dihydrotoxiferine behaves in a completely analogous manner to give *C*-alkaloid D (53), *C*-curarine (= *C*-curarine I) (54), *C*-calebassine (55), and the structurally unknown lumi-dihydrotoxiferine I,[24] which has so far not been isolated from natural sources. Also unknown to date are the structures of the naturally occurring further oxidation products of *C*-alkaloid D, namely *C*-alkaloid BL and *C*-venezueline.[25] *C*-Alkaloid G (56) and *C*-alkaloid F (57) can be prepared from *C*-alkaloid H.

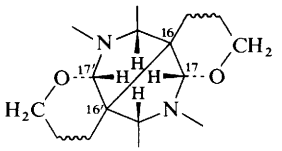
[24] F. Berlage, K. Bernauer, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1958, **41**, 683.
[25] H.-D. Schroeder, unpublished results; see M. Hesse, Dissertation, Universität Zürich 1964.

Chart C_{40}-*Alkaloid Families*

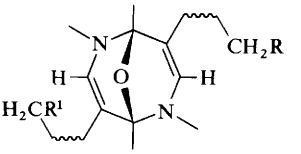


[a] H. D. Schroeder, unpublished results; see M. Hesse, Dissertation, Universität Zürich 1964.

The Chart indicates those members of the three families which with respect to structure, chemical behaviour, u.v., i.r., and n.m.r. spectra, and colour reactions are extremely similar. The alkaloids thus depicted differ only in the oxidation states of C(18) and C(18′): *C*-alkaloid A (52) possesses a hydroxy-group at each of these two centres, *C*-alkaloid F (57) at only one, and *C*-calebassine (55) at neither. The same relationship holds in the same order for *C*-alkaloid E (51), *C*-alkaloid G (56), and *C*-curarine (54). *C*-Alkaloid D (53) [no OH group at C(18) or C(18′)] has hydroxy-functions at C(17) and C(17′). In caracurine II dimetho-salt (50) these are displaced by the C(18)- and C(18′)-hydroxy-groups, resulting in two seven-membered ether rings which are also present in caracurine V dimetho-salt (39).



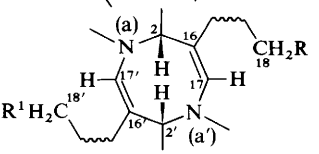
(50), Caracurine II dimetho-salt



(51) R = R¹ = OH; *C*-Alkaloid E
(54) R = R¹ = H; *C*-Curarine
(56) R = H; R¹ = OH; *C*-Alkaloid G

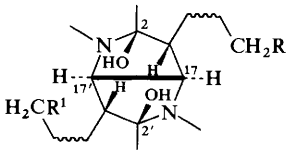
[O]

[O]

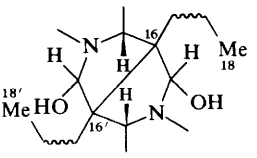


(38) R = R¹ = OH; *C*-Toxiferine
(46) R = R¹ = H; *C*-Dihydrotoxiferine
(49) R = H; R¹ = OH; *C*-Alkaloid H

[O]



(52) R = R¹ = OH; *C*-Alkaloid A
(55) R = R¹ = H; *C*-Calebassine
(57) R = H; R¹ = OH; *C*-Alkaloid F



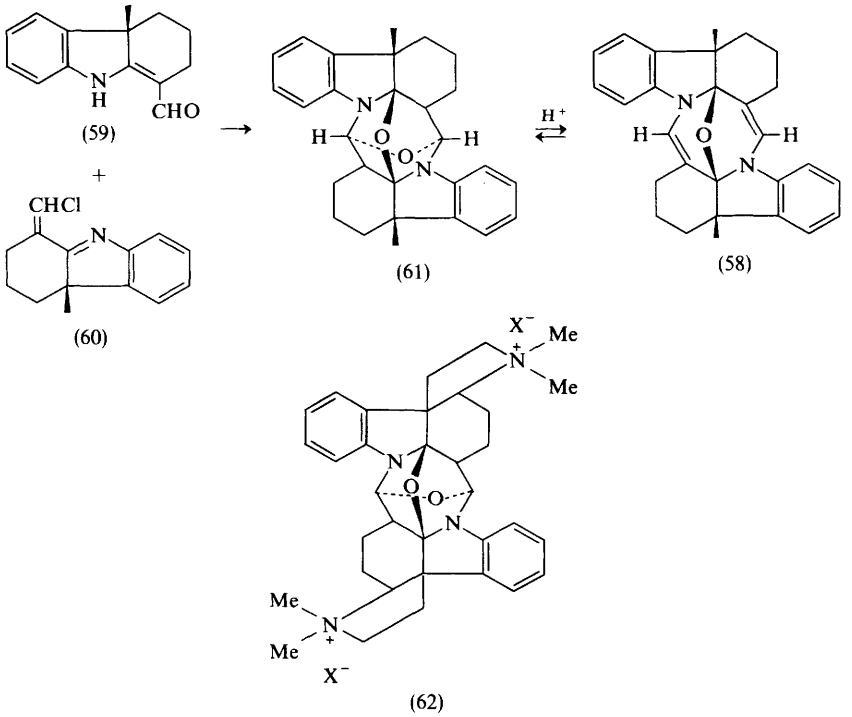
(53), *C*-Alkaloid D

Scheme 2

The synthesis of the calabash alkaloids possessing a more highly oxidised central ring is therefore possible from *C*-toxiferine and its relatives. A model for *C*-curarine (54), namely (58), has recently been synthesised.[26] Condensa-

[26] H. Fritz and R. Oehl, *Angew. Chem.*, 1966, **78**, 978.

tion of compounds (59) and (60) in ether gives (61), which under the influence of methanolic hydrochloric acid equilibrates with the dehydration product (58). The latter, which possesses the same central oxygen-bridged diazacyclo-octadiene ring as *C*-curarine (54), has a u.v. spectrum and a ceric sulphate colour reaction identical to those of the natural alkaloid. In an analogous manner, but with starting compounds possessing an extra fused pyrrolidine ring, the model (62) has also been prepared.[27]



The presentation here has been primarily concerned with the synthetic relationships between the 'dimeric' calabash-curare alkaloids. Literature is only cited when it is not contained in the recently published review articles.[17–19] In these works all the arguments leading to the structural classification of the alkaloids are fully discussed and the important contributions of the schools of H. Wieland and P. Karrer indicated.

It remains to be noted that recently *C*-dihydrotoxiferine (46), *C*-calebassine (55), *C*-toxiferine (38), *C*-alkaloid A (52), and *C*-alkaloid E (51) have been synthesised, specifically labelled at C(17) and C(17′) with deuterium. N.m.r. analysis[28]

[27] H. Fritz and G. Rubach, *Annalen*, 1968, **715**, 135.
[28] M. Grdinic, D. A. Nelson, and V. Boekelheide, *J. Amer. Chem. Soc.*, 1964, **86**, 3357.

confirmed in every detail the previously accepted interpretation of the spectra of these compounds.

Complete *X*-ray analyses of caracurine II dimetho-salt (50)[29] and *C*-calebassine (55)[30] have been carried out.

Acid-catalysed Isomerisations of Calabash-curare Alkaloids.—As has been described, *C*-toxiferine (38), *C*-dihydrotoxiferine (46), and *C*-alkaloid H (49), under the influence of aqueous acid, are readily cleaved *via* a retro-aldehyde–ammonia addition, into their two 'halves'. This ready cleavage was a key reaction for the elucidation of the structures of these alkaloids. In contrast, the more highly oxidised forms [caracurine II dimetho-salt (50) and *C*-alkaloid D (53), *C*-alkaloid E (51), and *C*-curarine (54),* *C*-alkaloid A (52), and *C*-calebassine (55), and their relatives] do not undergo breakdown into the two components but are preferentially isomerised. These isomerisations have been studied in most detail in the cases of *C*-calebassine (55) and *C*-curarine (54).

Anhydro-isocalebassine. When heated in strong mineral acid, *C*-calebassine salts (55, $C_{40}H_{48}O_2N_4^{2+}2X^-$) are irreversibly converted into yellow crystalline compounds of molecular formula $C_{40}H_{47}ON_4^{3+}3X^-H_2O$.†[31] These products, originally termed 'isocalebassines', are now known to be anhydro-isocalebassine hydro-salts. They have been assigned the formula (63H).‡[32] Alkaline dimethyl sulphate converts (63H) into anhydro-isocalebassine methyl ether (64, $C_{41}H_{48}ON_4^{2+}$), the di-iodide of which has been subjected to *X*-ray analysis.[32] The protonated form (64H), which possesses a cyanine system, exhibits practically the same u.v. absorption as (63H). Whereas (64) in alkaline solution shows no change, (63H) in 0.1N alkali shows a spectrum which in character corresponds to those exhibited by (63H) and (64H) in mineral acid. The species present in alkaline solution has been formulated as an anionic cyanine system (65). The reaction is reversible. In Scheme 3 a probable mode of formation of (63H) is depicted. An intermediate is the isolable dicationic pyrrole derivative (66), which is also formed on heating *C*-calebassine in glacial acetic acid.

At pH 4—7 (63H) is extremely sensitive to oxygen. By reaction with one mole of oxygen a red crystalline product with a merocyanine chromophore is formed, for which constitution (67) has been proposed.[32]

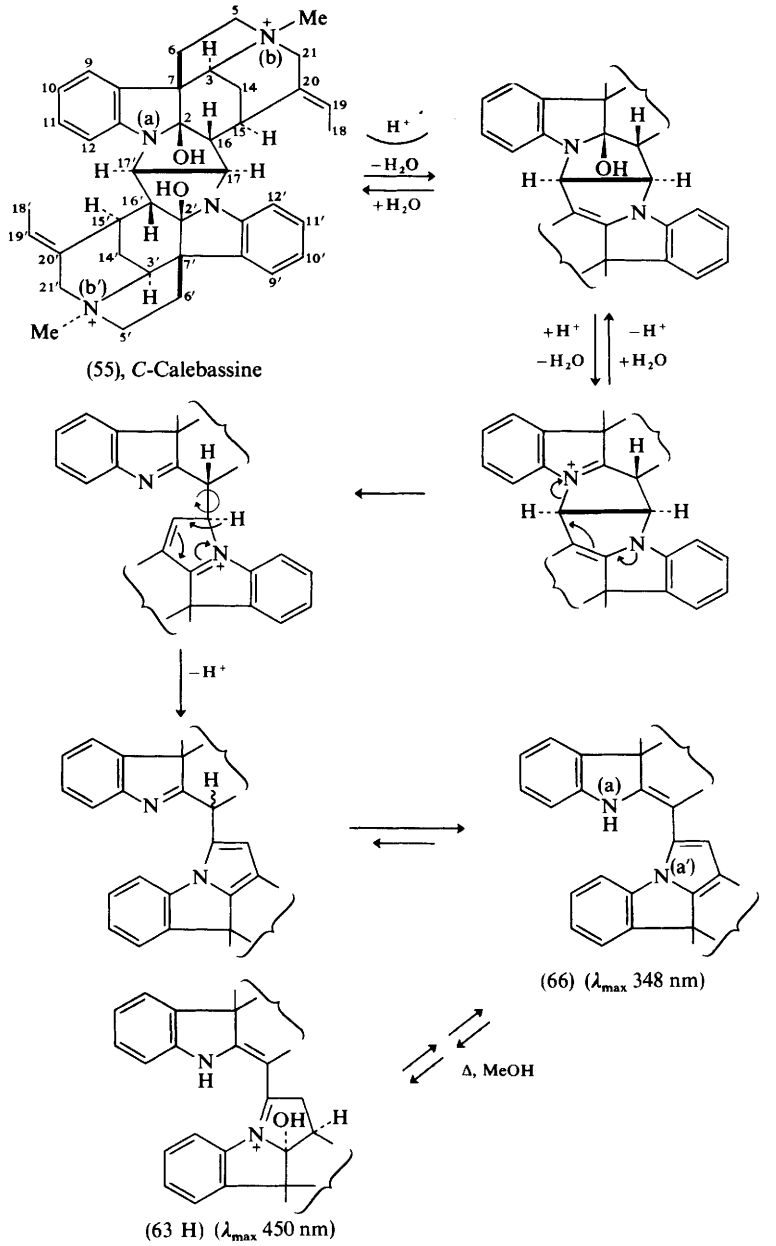
These extremely facile acid-catalysed isomerisations of the central part of the *C*-calebassine molecule are remarkable examples of chemical behaviour arising specifically out of the nature of the 'dimeric' linkage.

[29] A. T. McPhail and G. A. Sim, *Proc. Chem. Soc.*, 1961, 416.
[30] M. Fehlmann, H. Koyama, and A. Niggli, *Helv. Chim. Acta*, 1965, **48**, 303.
[31] K. Bernauer, E. Bächli, H. Schmid, and P. Karrer, *Angew. Chem.* 1957, **69**, 59.
[32] K. W. Gemmell, J. M. Robertson, G. A. Sim, K. Bernauer, A. Guggisberg, M. Hesse, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1969, **52**, 689.

* In addition to 'dimeric' isomerisation products, hydrogen bromide treatment of *C*-curarine yields the monomeric curare alkaloid *C*-fluorocurarine ($C_{20}H_{23}ON_2^+$) in low yield.[19]

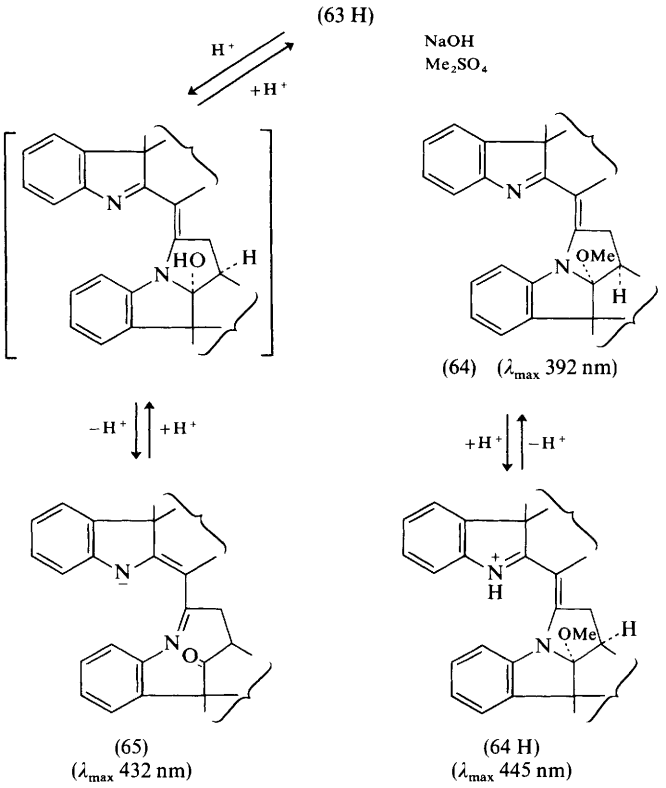
† *C*-Alkaloids E and F show similar behaviour.[31]

‡ H = protonated, tricationic form.

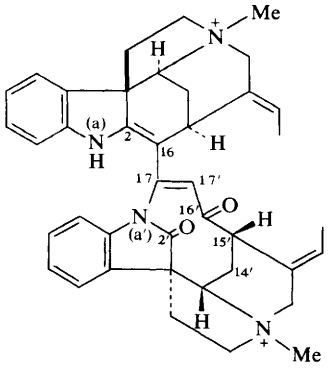


Scheme 3*

* The anions X^- have been omitted from the formulae.



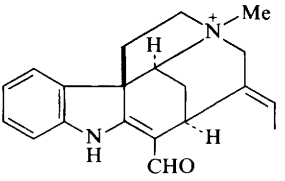
Scheme 3 (contd.)



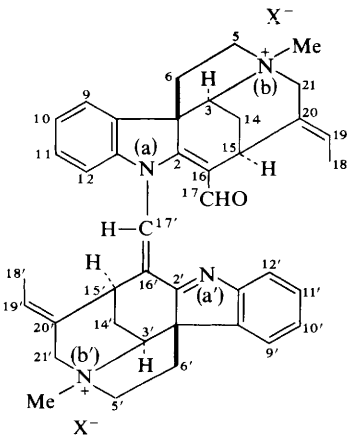
Oxidation product (67)

The Ultracurines. Treatment of *C*-curarine (54) with hot concentrated hydrochloric acid (5 hr; 60 °C) gives, as well as *C*-fluorocurarine (68), the so-called ultracurine A and other compounds.[33] Ultracurine A, when heated with stronger acid, is partly broken down into *C*-fluorocurarine.[34] The structure (69) has been proposed for ultracurine A,[35] for which combustion analyses indicate the molecular formula* $C_{40}H_{44}ON_4^{2+}$.[36] The model compound (70) shows u.v. absorption similar to that of ultracurine A.[35]

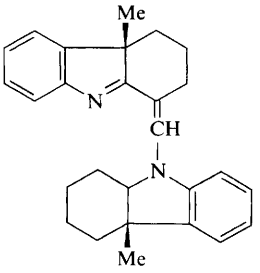
In 5N-HCl the long wavelength maximum in the spectrum of ultracurine A is shifted from 359 nm to *ca.* 406 nm, and in 10N-HCl to 416 nm.[36] The latter



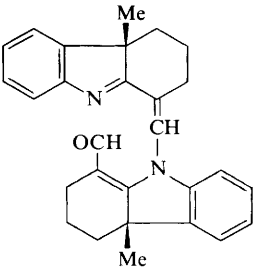
(68), *C*-Fluorocurarine



(69)



(70)



(71)

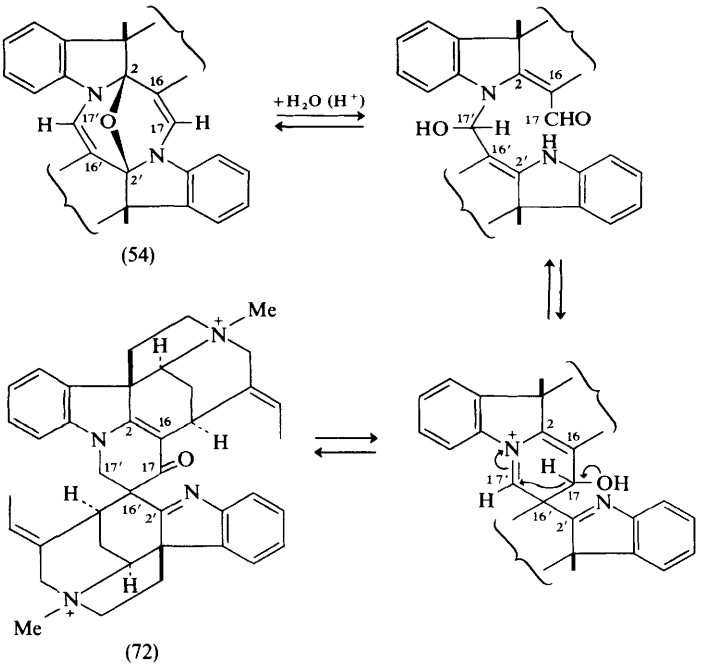
[33] H. Fritz and H. Meyer, *Annalen*, 1958, **617**, 162.
[34] H. Fritz, H. Meyer, and T. Wieland, *Annalen*, 1960, **633**, 156.
[35] H. Fritz, A. Krekel, and H. Meyer, *Annalen*, 1963, **664**, 188.
[36] J. Nagyvàry, Dissertation, Universität Zürich 1964.

* Ultracurine A and its derivatives, in the form of their dichlorides, do not give mass spectra of any value.

spectrum can be approximately simulated by mixing the spectra of the model compound (70) and its perchlorate in the molar ratio 2 : 1. However, model compound (71),[35] whose chromophore corresponds more closely to that of (69), shows a u.v. absorption similar to that of an α-methylene-indoline in neutral solution and already in 0.1N-HCl a maximum at 450 nm is observed. The curve does not correspond to that of ultracurine A.

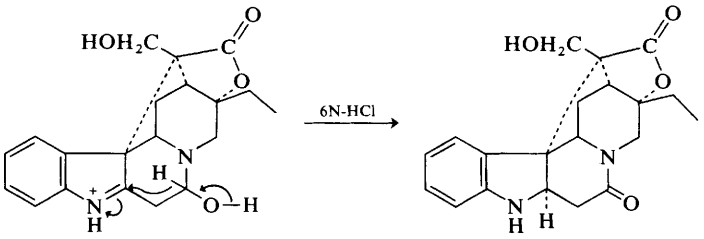
In the n.m.r. spectrum ($CDCl_3$) of the model compound (71) the signals due to the aldehyde and vinyl protons occur as singlets in the 5.5 p.p.m. region (in D_2O *ca.* 6—6.5 p.p.m.).*

The 60 MHz n.m.r. spectrum of ultracurine A dichloride (D_2O) shows signals due to eight aromatic protons in the region 6.8—7.8 p.p.m. The quartets of the vinyl protons at C(19) and C(19′) appear at somewhat different frequencies between 5.6 and 6.3 p.p.m., thus demonstrating the unsymmetrical nature of the molecule; the two *C*-methyl group signals are observed as overlapping doublets at 1.65 p.p.m. Apart from the aromatic and vinyl signals already mentioned, no further absorption is present between 4.8 and 20 p.p.m., *i.e.* no signals which could be attributed to the hydrogens at C(17) and C(17′) in formula (69) are present. This and further evidence appear to exclude structure (69) for ultracurine A.



Scheme 4

* The aldehyde signal for *C*-fluorocurarine chloride (D_2O) is observed at 9.3 p.p.m.



(73) (74)

The following proposals are largely based on experiments published in a thesis:[36] an analysis of the *C*-curarine (54) molecule shows that centres 2,17,2′, and 17′ are electrophilic, centres 16 and 16′ nucleophilic. The u.v. spectrum of ultracurine A is extremely similar to that of *C*-fluorocurarine chloride (68) and its $N_{(a)}$-methyl derivative;[37] if one assumes that no skeletal rearrangement of the two 'halves' has taken place, structure (72) appears to be a viable possibility for ultracurine A (Scheme 4). A precedent exists for the 1,3-hydride shift [(73) → (74)].[38] This hydrogen shift must be reversible, since on vigorous acid treatment ultracurine A gives some *C*-fluorocurarine (68). The question now arises as to whether the properties and known chemical behaviour of ultracurine A can be rationalised in terms of structure (72). Protonation of the ketonic oxygen explains the reversible 57 nm bathochromic shift of the u.v. spectrum in acid solution. *C*-Fluorocurarine (68) and its $N_{(a)}$-methyl derivative in concentrated hydrochloric acid show a bathochromic shift of 10 nm. This quantitative difference in behaviour could be due to (*a*) the different nature of the oxygen (ketone as opposed to aldehyde) and (*b*) the accommodation of the merocyanine system in a six-membered ring.*

The u.v. spectrum of ultracurine A is similar to the addition curve of a *C*-fluorocurarine (68) chromophore and that of an indolenine. On dissolving in a little concentrated hydrochloric acid followed by addition of alkali, or by warming at pH 5, ultracurine A is converted to ultracurine D, which from analytical data appears to be a hydration product.[36] Its u.v. spectrum represents an addition of *C*-fluorocurarine (68) and indoline chromophores. Structure (75) can therefore be assigned to ultracurine D.†

Reduction of ultracurine A with zinc–copper powder in dilute sulphuric acid, or with sodium borohydride at pH 8, gives the so-called reduction product 1 (76, $C_{40}H_{46}ON_4^{2+}$). This substance exhibits a u.v. spectrum very similar to

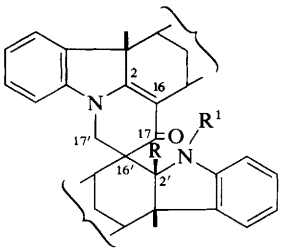
[37] W. v. Philipsborn, H. Meyer, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1958, **41**, 1257.

[38] A. A. Gorman, Thesis, University of Manchester 1964.

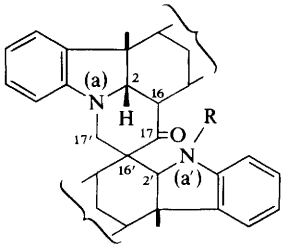
* A similar bathochromic shift is shown by the vinylogous acid amide chromophore of the oxidation product (67). Protonation or quaternisation of the model compound (70) also results in a bathochromic shift of 57 nm.

† If formula (69) were correct for ultracurine A, the addition of water would have to take place at the C(2′)–$N_{(a')}$ double bond.

that of ultracurine D (75). Substraction of an indoline spectrum gives a curve of the *C*-fluorocurarine (68) type. In 5N-HCl the long wavelength maximum is shifted by 21 nm. Acetylation of reduction product 1 gives an *N*-acetyl derivative (77) (carbonyl absorption at 1653 cm^{-1})* whose u.v. absorption corresponds to an addition of *C*-fluorocurarine (68) and *N*-acyl-indoline absorptions. In strong acid the long wavelength band undergoes a small bathochromic shift of 5 nm.



(75) R = OH; R^1 = H
(76) R = R^1 = H
(77) R = H; R^1 = Ac



(78) R = H
(79) R = Ac

Vigorous reduction of either ultracurine A or reduction product 1 with zinc in sulphuric acid gives reduction product 2 (78, $C_{40}H_{48}ON_4^{2+}$). Its u.v. spectrum is that of an indoline, *i.e.* both components possess an indoline chromophore. In the i.r. a carbonyl band absorbs at 1695 cm^{-1}. The n.m.r. spectrum shows no aldehyde proton resonance. Acetylation of reduction product 2 gives a mono *N*-acetyl derivative (79) whose i.r. spectrum shows carbonyl absorption at 1698 and 1656 cm^{-1}. The u.v. spectrum is an addition of indoline and *N*-acyl-indoline chromophores.†

Ultracurine A (72), ultracurine D (75), reduction product 1 (76), and its *N*-acetyl derivative (77) all show i.r. bands characteristic of the $>N-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$ grouping at 1658—1664 and 1629—1634 cm^{-1}. In $N_{(a)}$-methyl-*C*-fluorocurarine they occur at 1653 and 1621 cm^{-1}; the bands are absent from the spectrum of reduction product 2 (78).

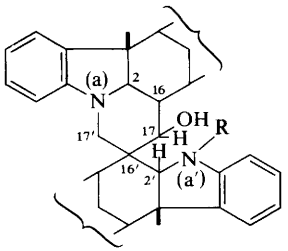
Sodium borohydride treatment of reduction product 2 gives reduction product 3 (80), a di-indoline, which shows no carbonyl absorption in its i.r. spectrum. The product gives only a mono-*N*-acetyl derivative (81). The secondary hydroxy-group must be sterically hindered after acylation of the neighbouring nitrogen has taken place.‡

Treatment of ultracurine A with sodium borohydride in strongly alkaline medium (pH 11) yields reduction product 4 (82), an extremely acid-sensitive compound, which in neutral solution exhibits a u.v. spectrum typical of the super-

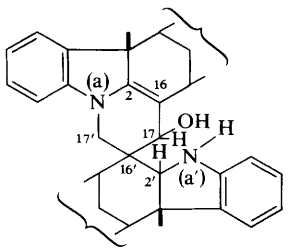
* All i.r. spectra in KBr.

† On the basis of structure (69) reduction product 2 would have to be formulated as a 2,16,2′,$N_{(a')}$,16′,17′-hexahydro-derivative, $C_{40}H_{50}ON_4^{2+}$.

‡ Based on structure (69) reduction product 3 would possess a primary hydroxy-group.



(80) R = H
(81) R = Ac



(82)

imposition of an indoline and an α-methylene-indoline chromophore. Its i.r. spectrum shows an enamine band at 1692 cm^{-1} and an indoline band at 1608 cm^{-1}. There is no carbonyl absorption.

Structure (72) thus satisfactorily accommodates the chemistry and physical properties of ultracurine A and its four reduction products.

3 Alkaloids with the Tubulosine Skeleton*

It is of interest that the five members of this group of bisindole alkaloids are distributed among three distinctly different plant families. Tubulosine (83), desoxytubulosine (84), 16-epitubulosine (= isotubulosine, 85), desmethyltubulosine (86) and alangimarckine (87) have all been found in *Alangium lamarckii* Thw. (Alangiaceae). Tubulosine (83) also occurs in *Pogonopus tubulosus* (D.C.) Schumann (Rubiaceae) and desoxytubulosine (84) in *Cassinopsis ilicifolia* Kuntze (Icacinaceae).

The structure of tubulosine (83) was derived principally from its mass spectrum which is similar to that of the *Ipecacuanha* alkaloid cephaeline and is characterised by main peaks at *m/e* 288, 274, 201, and 187,[46] *cf.* (83). Oxidation of (83) gives 4,5-dimethoxyphthalic acid. Condensation of the laevorotatory ester (88) of known absolute configuration with 5-benzyloxytryptamine yields the amide (89) which can be cyclised to the immonium derivative with phosphorus oxychloride; reduction with sodium borohydride followed by catalytic debenzylation gives tubulosine (83) [m.p. 283°C, $[\alpha]_D = -63°$ (pyridine)] and isotubulosine (85) [m.p. 164°C, $[\alpha]_D = -78°$ (pyridine)].[39] Tosylation and Raney-nickel desulphurisation of tubulosine (83) gives *N*-tosyl-desoxytubulosine.[40] The racemic desoxytubulosine (84) [$[\alpha]_D$ of the natural product = $-66°$ (pyridine)] has itself been synthesised from racemic (88) and tryptamine. The absolute configuration of centre 16 has been derived from an optical comparison of (−)-(84) with emetine.[41]

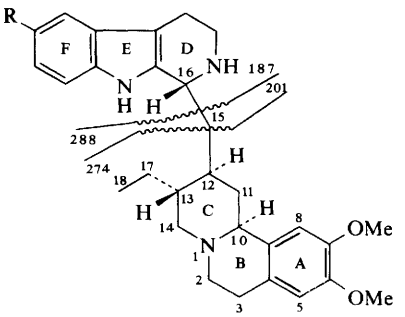
[39] H. T. Openshaw and N. Whittaker, *Chem. Comm.*, 1966, 131; *J. Chem. Soc.* (*C*), 1969, 89.

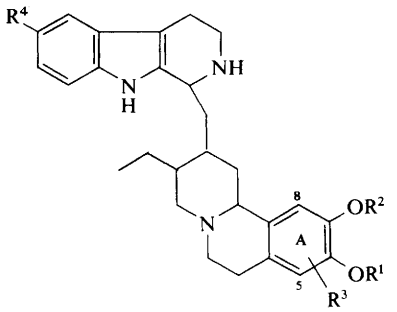
[40] H. Monteiro, H. Budzikiewicz, C. Djerassi, R. R. Arndt, and W. H. Baarschers, *Chem. Comm.*, 1965, 317.

[41] A. R. Battersby, J. R. Merchant, E. A. Ruveda, and S. S. Salgar, *Chem. Comm.*, 1965, 315.

* Details concerning the occurrence and isolation of the following alkaloids are to be found under reference 1.

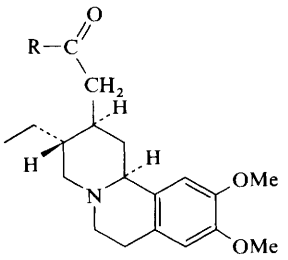
This centre in tubulosine (83), on the basis of the above correlation, has the same chirality as in the desoxy-compound (−)-(84).



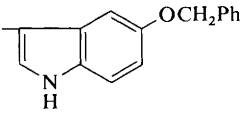


(83) R = OH; Tubulosine
(84) R = H; Desoxytubulosine
(85) R = OH, 16-epi; Isotubulosine

(86) R^1 = Me; R^2 = H or *vice versa*;
R^3 = H; R^4 = OH; Desmethyltubulosine
(87) R^1 = R^2 = Me; R^3 = OH at C(5) or C(8); R^4 = H; Alangimarckine



(88) R = OEt
(89) R = —NH—CH_2—CH_2—
(90) R = H



A base, isolated from *A. lamarckii*, has been shown to be identical with 16-epitubulosine (= isotubulosine, 85)[39,42] and in the same plant desmethyltubulosine (86) has been found, which on methylation yields *O*-methyltubulosine.[43] This species also contains yet another isomer of tubulosine (83), namely alangimarckine (87),[44] which has been shown from mass spectral and n.m.r.

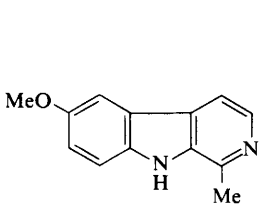
[42] A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Letters*, 1966, 5077.
[43] A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Letters*, 1966, 1081.
[44] A. R. Battersby, R. S. Kapil, D. S. Bhakumi, S. P. Popli, J. R. Merchant, and S. S. Salgar, *Tetrahedron Letters*, 1966, 4965.

evidence to have the phenolic hydroxy-group at either C(5) or C(8). A singlet at 6.24 p.p.m. for the proton on ring A is observed in the n.m.r. spectrum, *cf.* ref. 45. It would appear probable that (86) and (87) possess the same stereochemistry as (83) and (85).

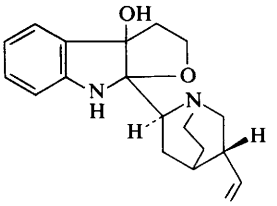
From a biogenetic standpoint these bases can be considered to be built up from protoemetine (90) and tryptamine precursors.[46]

4 Cinchophyllamine and Isocinchophyllamine

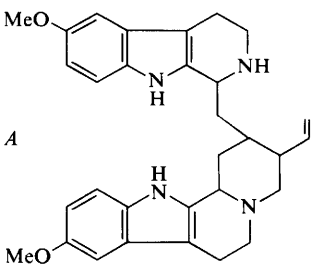
Cinchophyllamine (91) and isocinchophyllamine (92), molecular formulae $C_{31}H_{36}O_2N_4$, have been isolated along with quinamine (93) from the leaves of *Cinchona ledgeriana* Moens (Rubiaceae).*[47] The two alkaloids each possess two 5-methoxyindole chromophores per molecule (u.v. and n.m.r. evidence). Dehydrogenation gives 7-methoxyharman (94).[48] Of the two basic nitrogen



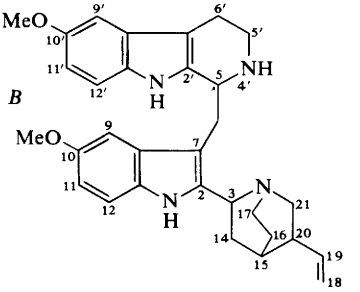
(94)



(93), Quinamine



(91)



(92)

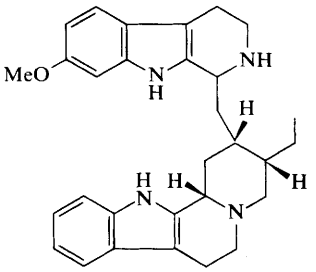
[45] D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *Chem. Comm.*, 1966, 294; A. Guggisberg, M. Hesse, H. Schmid, H. Böhm, H. Rönsch, and K. Mothes, *Helv. Chim. Acta*, 1967, **50**, 621.

[46] P. Brauchli, V. Deulofeu, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 1895.

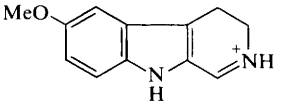
[47] J. Le Men, C. Kan, P. Potier, and M.-M. Janot, *Ann. pharm. franc.*, 1965, **23**, 691.

[48] P. Potier, C. Kan, J. Le Men, M.-M. Janot, H. Budzikiewicz, and C. Djerassi, *Bull. Soc. chim. France*, 1966, 2309.

* A fourth alkaloid, cinchophylline ($C_{31}H_{36}O_2N_4$), of unknown structure also occurs in the plant.[1]



(95)



a
(*m/e* 201)

atoms present, one is secondary, the other tertiary. A vinyl side-chain which can be hydrogenated is also present.

In the mass spectrum of both alkaloids and their dihydro-derivatives appears a fragment ion peak at *m/e* 201 (*a*). In the spectrum of *N*-methylcinchophyllamine, obtained by lithium aluminium hydride reduction of the *N*-formyl derivative, the peak is shifted to *m/e* 215.

These observations, together with the co-occurrence of quinamine (93) and the occurrence of aricine (heteroyohimbine type) in *Cinchona pelletieriana* Wedd. (*C. pubescens* Vahl),[1] led to the proposal of the alternative structures *A* and *B* for these probably stereoisomeric alkaloids.

A model (95) for structure *A* has been obtained by condensation of 6-methoxytryptamine with dihydrocorynantheal. The mass spectrum of this compound is significantly different from those of the dihydro-derivatives of (91) and (92), although on the other hand the same is true of the mass spectra of (91) and (92) themselves. However, structure *B* for cinchophyllamine (91) and isocinchophyllamine (92), thought to be C(3)-epimers, is preferred to structure *A*.[48]

5 The Roxburghines

Until recently only monomeric indole and oxindole alkaloids had been isolated from the bark and leaves of *Uncaria gambir* Roxb. (Rubiaceae). Amongst these were alkaloids of the corynantheine and yohimbine types.[49] However, from a different batch of plant material five new isomeric alkaloids, the roxburghines A—E, $C_{31}H_{32}O_2N_4$, have been isolated in 0.0005—0.005% yield.[50]

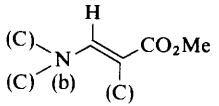
The major alkaloid, roxburghine D, has been assigned the structure (96).* The u.v. spectrum of this base is a superimposition of the absorptions of two tetrahydro-β-carbolines and one β-alkylamino-acrylic ester. The latter is responsible for strong i.r. bands at 1661 and 1613 cm^{-1} (KBr) and is contained in the

[49] L. Merlini, R. Mondelli, G. Nasini, and M. Hesse, *Tetrahedron*, 1967, **23**, 3129; L. Merlini and G. Nasini, *Gazzetta*, 1967, **97**, 1915; L. Merlini, R. Mondelli, G. Nasini, and M. Hesse, *Tetrahedron Letters*, 1967, 1571.

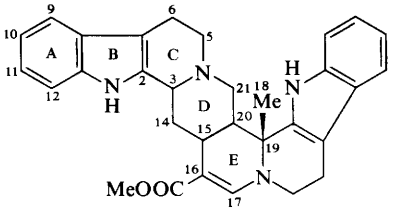
[50] L. Merlini, R. Mondelli, G. Nasini, and M. Hesse, *Tetrahedron*, 1970, **26**, 2259.

* The configuration shown is relative.

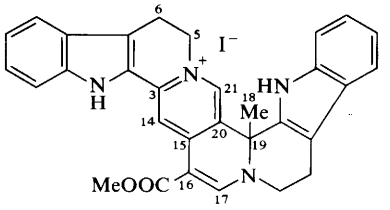
part formula (n.m.r. evidence):



The two indolic $N_{(a)}$-atoms are unsubstituted, the two $N_{(b)}$-atoms tertiary (spectroscopic and D-exchange evidence). The single *C*-methyl group is tertiary.



(96), Roxburghine D



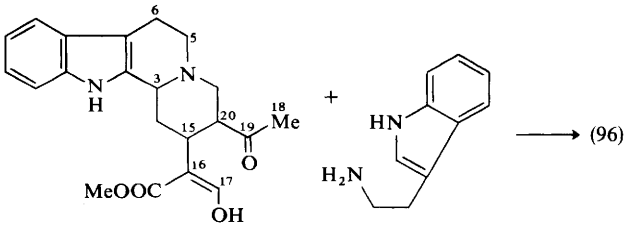
(97)

Vigorous dehydrogenations of roxburghine D give 3-ethylindole and harman as the only identifiable products. In contrast, treatment with iodine in sodium acetate yields a compound $C_{31}H_{27}O_2N_4{}^+I^-$ (97). Clearly this process involves the dehydrogenation of an *N*-alkylpiperidine to an *N*-alkylpyridinium salt. The orange, optically-active dehydrogenation product exhibits a cyanine absorption spectrum with intense maxima at 316 and 430 nm which indicates the presence of a highly conjugated chromophoric system, probably a 2,2′-pyridinium-indole chromophore (long wavelength maximum at *ca.* 385 nm[51]) with additional conjugation. The n.m.r. spectrum of this product shows the presence of two indolic NH groups, eight aromatic protons, the tertiary methyl group, and the β-amino-acrylic ester grouping with a one-proton singlet in the 8.5 p.p.m. region. In this region two other one-proton signals are apparent. Remaining are eight aliphatic protons which by careful analysis were shown to be arranged in two indole–CH_2–CH_2–N(b)< sequences. On the basis of these data two possible

[51] G. A. Swan, *J. Chem. Soc.*, 1958, 2038.

structures can be drawn for the cyanine-like dehydrogenation product, (97) and the alternative in which C(19) and C(16) are bonded to C(15) and C(20) respectively. For roxburghine D itself this leads to (96) or the corresponding alternative. It has been possible by n.m.r. spectroscopy to analyse completely the proton system of ring D of the latter, and thus confirm the proposed substitution, and at the same time determine the relative configurations of the centres 3, 15, and 20. Rings C and D constitute a *cis*-quinolizidine system.

The roxburghines D and C on the one hand, and B and E on the other, give dehydrogenation products which differ only with respect to the chirality of C(19). The difference between B and E lies only in the configuration at C(3), since E is converted to B when heated in acetic acid. Centre 3 is the only invertible centre under these conditions. The depicted mode of linkage between rings D and E (196) is supported by the fact that the C(15)- and C(17)-protons are coupled with each other (in the alternative formula such coupling *via* C(16) and C(20) would be extremely unlikely). Biogenetic arguments favour formula (96); obvious precursors would be a corynantheine-derivative (98) and tryptamine. In the alternative case the precursor would possess a rearranged corynantheine skeleton of a type so far not encountered in the indole alkaloid field.



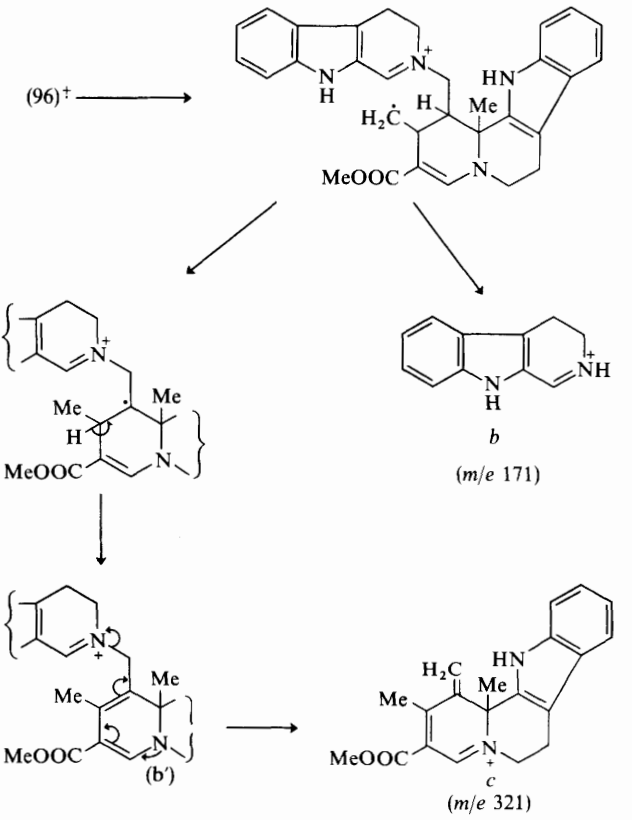
(98)

The mass spectrum of roxburghine D is in agreement with the proposed structure (96). Analysis shows that fragmentation of the molecule in all cases involves participation of the nitrogen $N_{(b')}$; a characteristic breakdown process is depicted in Scheme 5.

It is noteworthy that the five roxburghines, at least three of which are known to be stereoisomers, give distinctly different mass spectra.[50]

6 Haplophytine

This insecticidal alkaloid (99, $C_{37}H_{40}O_7N_4$) has been isolated from *Haplophyton cimicidum* A.DC. (Apocynaceae). It contains two basic nitrogens and a phenolic hydroxy-group. Acid-catalysed cleavage leads to the base (100), whose structure follows from spectral data, and in particular from a comparison of its mass



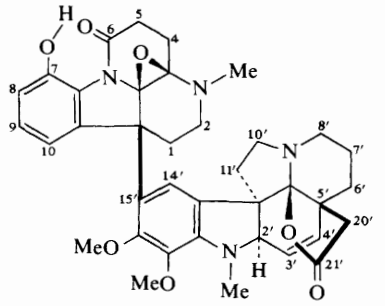
Scheme 5

spectrum with that of cimicidine (101).[52] In haplophytine itself the additional $C_{15}H_{15}O_3N_2$ residue can be shown to be attached to C(15').

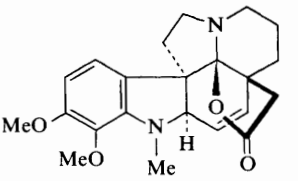
The dihydrobromide of the alkaloid has been subjected to *X*-ray analysis and its structure and absolute configuration shown to be that depicted in (102). On the basis of the molecular formula, the ditertiary nature of the alkaloid, and the fact that at pH 8 (102) is converted into haplophytine, the complete structure (99) follows for the alkaloid.[52]

The upper half of the molecule is related to canthinone (103).[1] The >N—C(=O)—C—N< grouping is unique. The chirality of the lower 'half' corresponds to that of (−)-aspidospermine (104).[1]

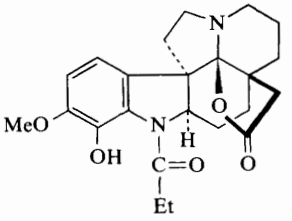
[52] I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, P. Yates, D. E. Zacharias, G. A. Jeffrey, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *J. Amer. Chem. Soc.*, 1967, **89**, 3061.



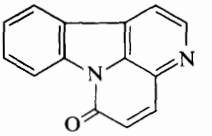
(99), Haplophytine



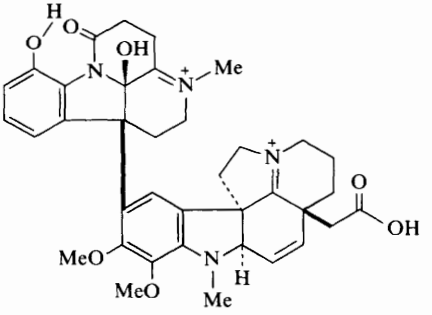
(100)



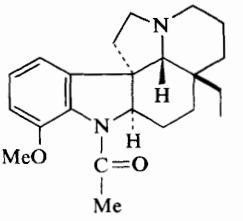
(101), Cimicidine



(103), Canthinone



(102)



(104), (−)-Aspidospermine

7 Geissospermine[53,54] and Geissolosimine[53]

Geissospermine (105).—The alkaloid was isolated as early as 1887[55] from the Brazilian Apocynaceae *Geissospermum laeve* (Vellozo) Baillon, synonymous with *G. laeve* Miers. and *G. vellozii* or *G. vellosii* Allem; its dimeric nature was recognised much later. Of historical interest are the comments of Bertho and Sarx

[53] R. H. F. Manske, 'The Alkaloids of Geissospermum Species,' in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII. The Indole Alkaloids, Academic Press, New York, 1965, p. 679.

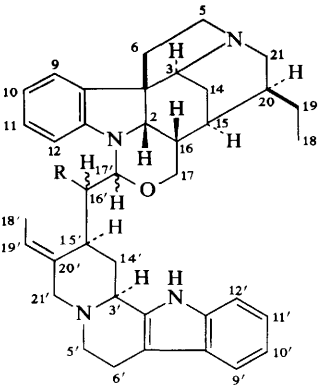
[54] M.-M. Janot, *Tetrahedron*, 1961, **14**, 113.

[55] O. Hesse, *Ber.*, 1877, **10**, 2162.

in 1944, that it gives colour reactions typical of both *Strychnos* and *Yohimbe* alkaloids.[56] In fact, the u.v. spectrum of geissospermine can be interpreted as a summation of an indole and an indoline chromophore.[57]

When heated with hydrochloric acid the alkaloid, $C_{40}H_{48}O_3N_4$, gives three monomeric bases, geissoschizoline (106), $C_{19}H_{26}ON_2$, geissoschizine (107), $C_{21}H_{24}O_3N_2$, and apogeissoschizine (108), $C_{21}H_{22}O_2N_2$. The yield of (107) and (108) corresponds to *ca.* 20% each of the theoretical value. Geissoschizoline (106) co-occurs with geissospermine in *G. laeve*.[58]

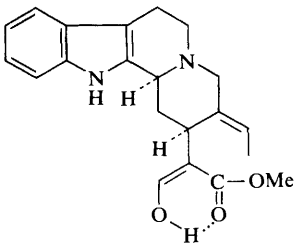
The structure of geissoschizine (107) (see Scheme 6) was principally established as follows:* cold concentrated hydrochloric acid treatment of (107) (5 min) yields, *via* demethoxycarbonylation, the aldehyde (109) which can be converted in the standard manner to the derivatives (110) (geissoschizol) and (111). Dehydrogenation (Pd–C) of (111) gives alstyrine (112). Similar treatment of the demethoxycarbonylated product from geissospermine (105) itself, namely (113) prepared by methanolic alkali treatment of (105), gives desmethylalstyrine (114). This result, together with the interpretation of spectral data, leads to structure (107) for geissoschizine.[60] Catalytic reduction of geissoschizol (110) leads to (−)-corynantheidol (115) of known absolute configuration, so that (107) represents the complete structure of geissoschizine.[61] When heated in glacial



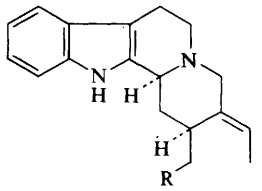
(105) R = CO_2Me; Geissospermine
(113) R = H

[56] A. Bertho and H. F. Sarx, *Annalen*, 1944, **556**, 22.
[57] K. Wiesner, W. Rideout, and J. A. Manson, *Experientia*, 1953, **9**, 369.
[58] H. Rapoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Amer. Chem. Soc.*, 1958, **80**, 1601.
[59] N. J. Dastoor, A. A. Gorman, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 213.
[60] H. Rapoport, R. J. Windgassen, N. A. Hughes, and T. P. Onak, *J. Amer. Chem. Soc.*, 1959, **81**, 3166.
[61] F. Puisieux, R. Goutarel, M.-M. Janot, and A. Le Hir, *Compt. rend.*, 1956, **242**, 2981.

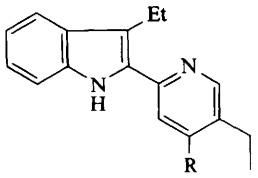
* As far as is known, all naturally occurring indole alkaloids possessing the ethylidene or hydroxy-ethylidene side chains have the geometric configuration shown [C(19)–Me *cis* to C(15)].[59]



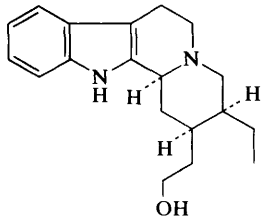
(107), Geissoschizine



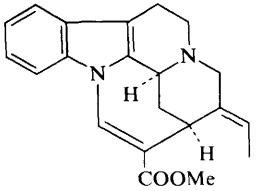
(109) R = CHO
(110) R = CH_2OH; Geissoschizol
(111) R = Me



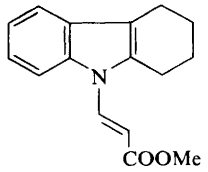
(112) R = Et; Alstyrine
(114) R = Me



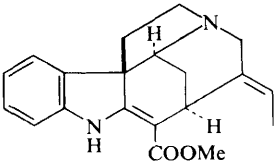
(115), (−)-Corynantheidol



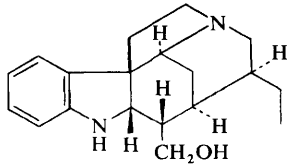
(108), Apogeissoschizine



(116)



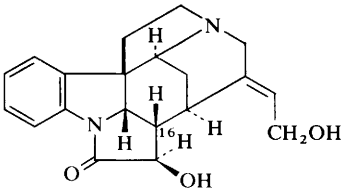
(117), (−)-Akuammicine



(106), Geissoschizoline

Scheme 6

acetic acid at 130 °C (18 hr), (−)-(110) and (−)-(115) are epimerised to the extent of 80% into their dextrorotatory 3-epi-forms.[59] Conversion of (107) to (110) therefore gives the kinetically-controlled product. Assuming this also to be the case for the acid cleavage of (105) to (107), it follows that C(3) in geissospermine (105) has the same configuration as in (110) (see later).



(118)

Apogeissoschizine (108) is an anhydro-geissoschizine; it is also formed from geissoschizine (107) by the action of concentrated hydrochloric acid,[61,62] although somewhat slower than from geissospermine (105) itself. It exhibits a u.v. spectrum very similar to that of the model compound (116).[62]

Geissoschizoline [= pereirine (106)] is an indoline derivative with a *Strychnos* carbon skeleton. The complete structure was elucidated by partial synthesis from (−)-akuammicine (117): the latter on reduction with zinc and acid forms 2β,16β-dihydroakuammicine which on lithium aluminium hydride reduction followed by catalytic hydrogenation gives geissoschizoline (106).[63] The base can also be obtained by degradation of the strychnine derivative (118).[64]

Since in geissospermine the grouping $H_3COOC-\underset{|}{C}=\underset{|}{C}-O-$ is absent and only one active hydrogen is present, only the amino-acetal structures (105) and (120) (Scheme 7) need to be considered for the alkaloid. Lithium aluminium hydride converts geissospermine into geissospermol (119, $C_{39}H_{50}O_2N_4$), in which both the ester and amino-acetal groupings have been reduced. The formation of this product, which forms an *OO*-diacetyl derivative, from (105) agrees well with the lithium aluminium hydride reduction of (121) to (122).[65] The geissospermol structure (119) does not, however, definitely exclude the alternative geissospermine structure (120) as shown in Scheme 7. The same holds for the partial synthesis of the alkaloid by condensation of geissoschizoline (106) with geissoschizine (107) in 10% acetic acid, which presumably proceeds by way of the intermediate (123) (Scheme 8).*[66]

In Scheme 8 the probable mode of formation of apogeissoschizine (108) *via* (123) and (124) is shown, evidence for which is the fact that geissoschizine (107) is converted much more slowly to (108) than is geissospermine (105) itself under identical conditions.[62]

[62] H. Rapoport, R. J. Windgassen, N. A. Hughes, and T. P. Onak, *J. Amer. Chem. Soc.*, 1960, **82**, 4404.

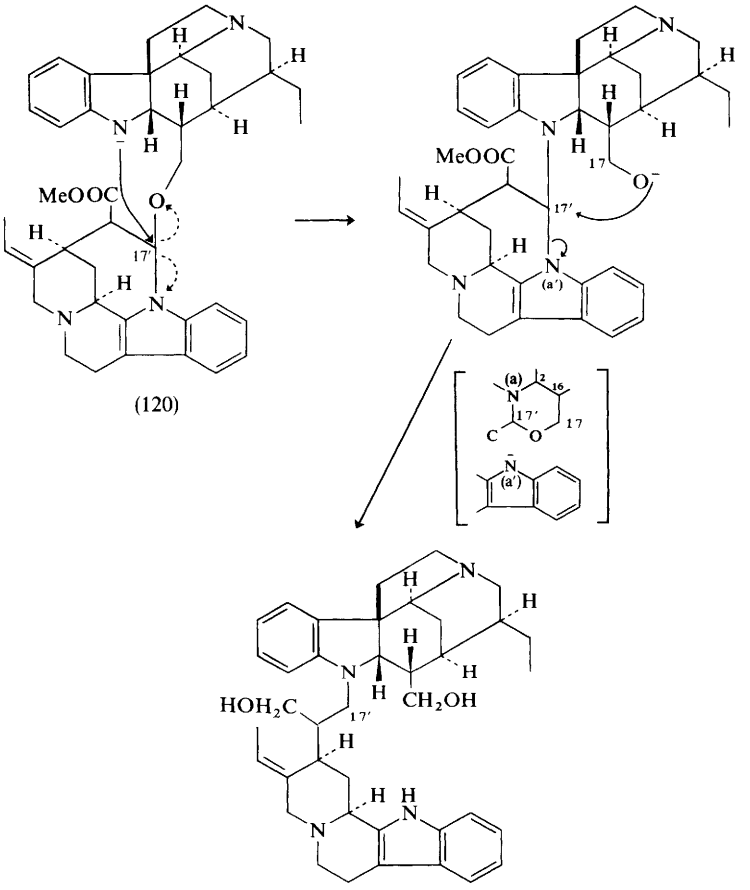
[63] M.-M. Janot, J. Le Men, A. Le Hir, J. Lévy, and F. Puisieux, *Compt. rend.*, 1960, **250**, 4383.

[64] J. R. Hymon and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 2067.

[65] F. Puisieux and A. Le Hir, *Compt. rend.*, 1961, **252**, 902.

[66] F. Puisieux, R. Goutarel, M.-M. Janot, J. Le Men, and A. Le Hir, *Compt. rend.*, 1960, **250**, 1285.

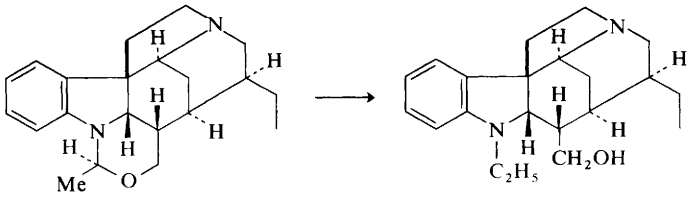
* To our knowledge the condensation of apogeissoschizine (108) with geissoschizoline (106) has not been investigated.



(120)

(119), Geissospermol

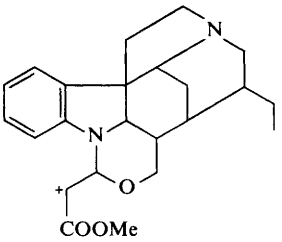
Scheme 7



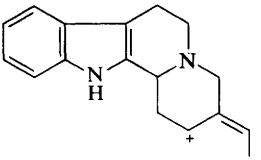
(121) (122)

Scheme 8

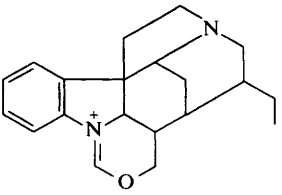
The observation that geissospermine, in contrast to geissoschizoline (106), cannot be acetylated favours structure (105). A more certain differentiation is offered by the mass spectrum of the 'dimer'.*[67] This contains peaks due to the fragments *m/e* 381 and 251, which result from cleavage of the allylically activated C(15′)–C(16′) bond and together make up the molecular weight of the alkaloid (M^+ = 632). If the cleavage is accompanied by a McLafferty rearrangement involving the hydrogen at C(17′) the fragment *m/e* 252 is formed. The base peak, *m/e* 309, clearly confirms the assigned structure and eliminates (120) as an alternative.



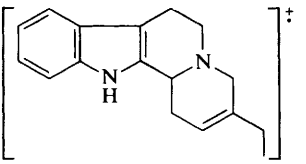
(*m/e* 381)



(*m/e* 251)



(*m/e* 309)



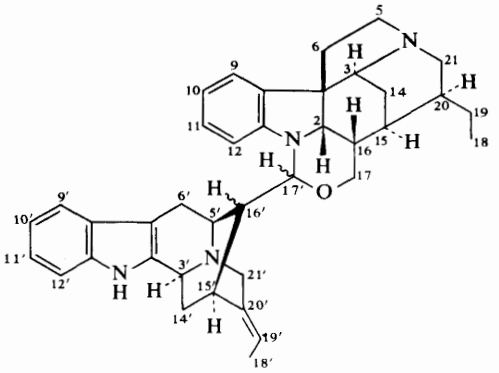
(*m/e* 252)

Geissolosimine (125).—The 'dimer' geissolosimine, $C_{38}H_{44}ON_4$, co-occurs with geissospermine in *G. vellosii*.[58] Its u.v. spectrum is superimposable on that of the latter. Cleavage with hydrochloric acid leads to geissoschizoline (106) and a second monomer, vellosimine (126), which is present as a minor alkaloid in *G. vellosii*.[58] The structure and absolute stereochemistry of vellosimine (126)[68] have been shown by correlation with normacusine B (= tombozine).

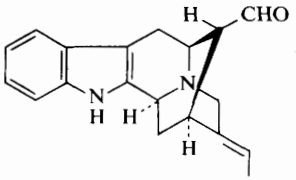
Geissolosimine (125) shows the same chemical behaviour as geissospermine (105) and an analogous synthesis has been performed. In the n.m.r. spectrum it

[67] M. Hesse, unpublished results.
[68] H. Rapoport and R. E. Moore, *J. Org. Chem.*, 1962, **27**, 2981.

* The spectrum shows the following peaks: *m/e* (%), 632, M^+ (3), 573(1), 494(1), 488(1), 382(1), 381(34), 309(100), 252(32), 251(32), 250(10), 249(14), 144(30).



(125), Geissolosimine



(126), Vellosimine

shows a doublet at 5.21 p.p.m. due to the carbinolamine ether proton at C(17′). The presence of this signal confirms the structure (125) shown for geissolosimine*.[68]

8 The Secamines and Presecamines

The Secamines.—From the leaves of *Rhazya stricta* Decaisne and *R. orientalis* A.DC. (Apocynaceae) three novel bisindole alkaloids, namely secamine (127), $C_{42}H_{52}O_4N_4$, dihydrosecamine (128), and tetrahydrosecamine (129), have recently been isolated in amorphous form.[69] The structural assignments of the three secamines, each of which is probably a mixture of stereoisomers, are based on the following arguments:[69] the bases each contain two simple indole chromophores and two methoxycarbonyl groupings, one of which is secondary, the other tertiary (D-exchange at 100 °C with MeONa–MeOD). Of the four nitrogen atoms one is secondary, the remainder tertiary (D-exchange in MeOD[70]). The mass spectrum of tetrahydrosecamine (129) is dominated by an extremely intense peak at *m/e* 126 ($C_8H_{16}N^+$) which corresponds to fragment *d*.

[69] D. A. Evans, G. F. Smith, G. N. Smith, and K. S. J. Stapleford, *Chem. Comm.*, 1968, 859.

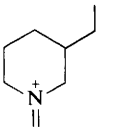
[70] V. Agwada, A. A. Gorman, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 1939.

* A structure corresponding to (120) is impossible on steric grounds.

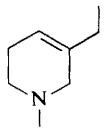
The Hofmann degradation of secamine dimethiodide yields *N*-methyl-3-ethyl-1,2,5,6-tetrahydropyridine (130). The *N*-substituted 3-ethyl-1,2,5,6-tetrahydropyridine skeleton occurs in secamine (127) itself twice (two vinylic protons; *m/e* 124 fragment in the mass spectrum = dehydro *d*) and in dihydrosecamine once (peaks at *m/e* 124 and 126). Correspondingly, tetrahydrosecamine (129) contains two 3-ethylpiperidine rings, dihydrosecamine (128) only one.

Alkaline hydrolysis of the two ester groups in tetrahydrosecamine (129) followed by heating in 1N-HCl gives, along with other products, the base (131). Reductive di-demethoxycarbonylation ($SnCl_2$–HCl; 100 °C) leads to (132) ($C_{38}H_{54}N_4$), whose structure has been confirmed by degradation and synthesis.

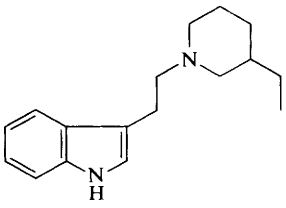
These results, together with the facile loss of two methoxycarbonyl functions, which indicates the presence of two indolylacetic ester residues, allow the postulation of the alternative structures (127a) and (127b) for secamine. These also readily accommodate the results of deuteriation experiments carried out in



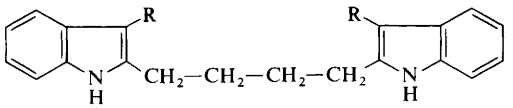
d
(*m/e* 126)



(130)



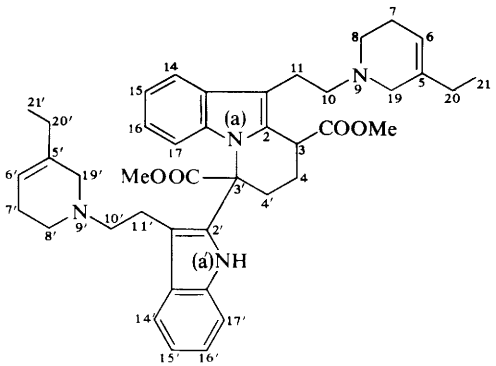
(131)

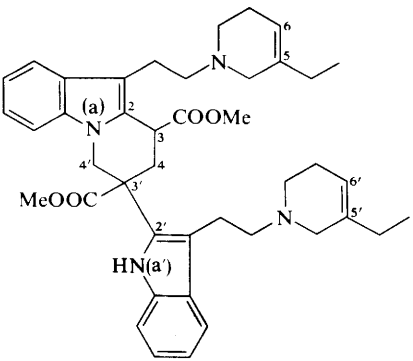


(132) R = $-CH_2-CH_2-N$

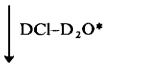
D_2O–DCl. Di-demethoxycarbonylation of tetrahydrosecamine (129) in D_2O–DCl gives, as the most highly deuteriated product, a base $C_{38}H_{39}D_{13}N_4$(*C*-deuteriation) (133a or 133b, R = D) as shown in Scheme 9. Of the thirteen *C*-deuteriums introduced eight are aromatic in character.[71] The remainder are

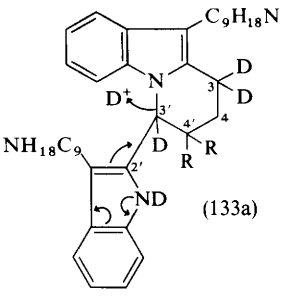
[71] T. Kishi, M. Hesse, W. Vetter, C. W. Gemenden, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 946.



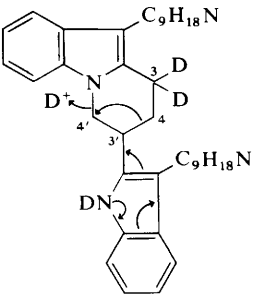


(127a) Secamine (127b)
(128a) 5,6- or 5′,6′-Dihydrosecamine (128b)
(129a) 5,5′,6,6′-Tetrahydrosecamine (129b)

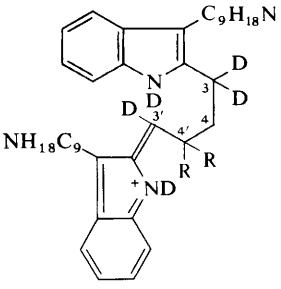




(133a)

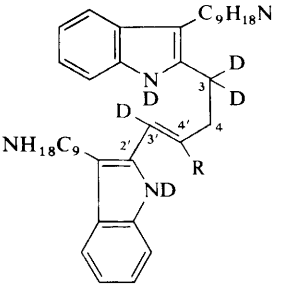


(133b)



(134)

in equilibrium; R = D



(135)

Scheme 9

* The aromatic deuterons are not marked.

localised in the central part of the molecule [two at C(3), two at C(4′), and one at C(3′); aspidospermine nomenclature]. One deuterium each at C(3) and C(3′) is introduced as a result of demethoxycarbonylation, the second by the known acid-catalysed exchange of α-indolylic protons. The two remaining deuteriums are probably introduced *via* the mechanism depicted in Scheme 9. These exchange reactions can be accommodated in terms of both structures (129a) and (129b) for tetrahydrosecamine.

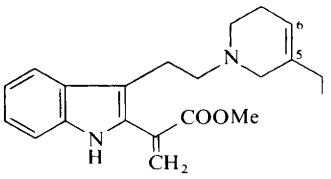
The formation of (131) could proceed *via* reaction paths involving initial protonation of C(2′) in (133a) or of C(2′) in the 3′,4′-hydrated form of (135).

Production of the base (132) on treatment of tetrahydrosecamine (129) with $SnCl_2$–HCl can be interpreted in terms of the reaction sequence (129) → (135) followed by reduction.

It has recently been shown that the secamines are formed on acid-catalysed rearrangement of the presecamines, and it is almost certain that their production, either within the plant or during the isolation process, involves this kind of rearrangement.

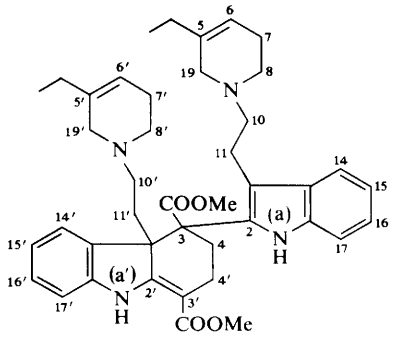
The Presecamines.—A second group of bisindole alkaloids, the presecamines [presecamine (138), dihydropresecamine, and tetrahydropresecamine] have been isolated from *R. stricta* and *R. orientalis.*[72] These alkaloids are isomeric with the corresponding secamines but no 'dimeric' molecular ion is observed in their mass spectra. Their 'dimeric' nature was recognised from their u.v. spectra which correspond to summations of indole and β-anilino-acrylic ester absorptions. The i.r. spectra show two N–H bands, characteristic β-anilino-acrylic ester bands, and saturated ester absorption.

The highest mass peak in the mass spectra of these 'dimers' corresponds to $M^+/2$, even at 120 °C and 15 eV. The fragmentation pattern for presecamine (138) is identical to that of compound (136) which has been named secodine.[72] This indicates the occurrence of a facile retro-Diels–Alder reaction: such a process can be carried out preparatively at 175 °C/0.2 mm to give secodine (136) from presecamine itself, and dihydrosecodine (137) from tetrahydropresecamine. The product (137) has been identified by direct comparison with synthetic material. On standing without solvent, (136) and (137) dimerise to give diastereoisomeric mixtures of the corresponding presecamines.

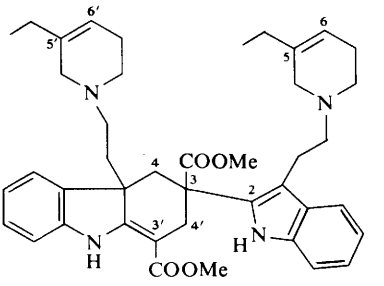


(136), Secodine
(137) 5,6-Dihydro

[72] G. A. Cordell, G. F. Smith, and G. N. Smith, *Chem. Comm.*, 1970, 191; R. T. Brown, G. F. Smith, K. S. J. Stapleford, and D. A. Taylor, *ibid.*, p. 190.



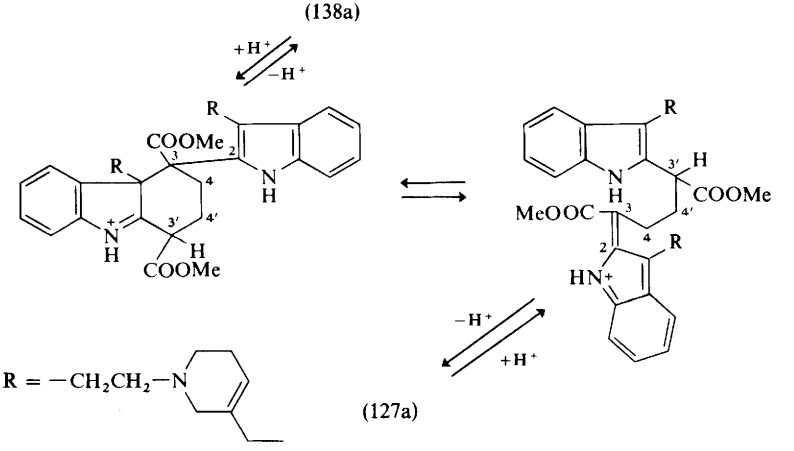
(138a)



(138b)

Presecamine
Dihydropresecamine = 5,6- or 5′,6′-dihydro
Tetrahydropresecamine = 5,5′,6,6′-tetrahydro

The two alternative structures, (138a) and (138b), suggested for presecamine by these results are supported by the fact that on standing in 2N aqueous HCl at room temperature for 15 min presecamine (138) and its tetrahydro-derivative are converted into a secamine (127) and a tetrahydrosecamine (129) respectively. This favours structure (138a) for presecamine, ring-opening as shown leading to (127a). A conversion of (138b) to the alternative secamine (127b) is certainly less plausible.



From a mechanistic viewpoint, therefore, structures (127a) and (138a) for secamine and presecamine are much more satisfactory than the alternatives (127b) and (138b). The question as to whether the sequence (136) and (137) →

presecamines → secamines occurs naturally, or only during extraction, has not to date been resolved.*

9 Alkaloids of the Voacamine Type†

A characteristic of the genera *Callichilia*, *Conopharyngia*, *Gabunia*, *Stemmadenia*, *Tabernaemontana*, and *Voacanga* of the Apocynaceae family is the presence of bisindole alkaloids of the voacamine type, the prototype of this group being voacamine itself. All these alkaloids are composed of a vobasine-like [vobasine, (139)] and an ibogamine-like [*e.g.* coronaridine, (140)] unit. The corresponding monomeric alkaloids occur frequently in the company of the 'dimers'. In all cases the nature of the linkage is the same and consequently the chemical behaviour very similar. To date, nine members of this group are known: apart from voacamine they are voacamidine, voacamidine $N_{(b)}$-oxide, 18′-demethoxycarbonyl-voacamine, voacorine, 20′-epivoacorine, conodurine, conoduramine and gabunine.[1]

Voacamine.[74]—The alkaloid (141, $C_{43}H_{52}O_5N_4$) contains an indole and a 5-methoxyindole chromophore. The functional groups present are: two tertiary $N_{(b)}$-atoms (pK'_a: 5.2 and 6.8), one of which carries a methyl group, two methoxycarbonyl functions, two indolic NH groups (D-exchange and n.m.r. evidence), an aromatic methoxy-group, and ethylidene and ethyl side-chains.

Acid-catalysed hydrolysis yields voacangine[1] (142, $C_{22}H_{28}O_3N_2$); the other 'half' cannot be isolated as a well-defined product.[75] Cleavage of voacamine with DCl–D_2O–MeOD gives 11,13,14-trideuteriovoacangine (mass spectral and n.m.r. evidence). This result indicates that the bond from the voacangine unit to the unknown part of voacamine is attached to one of the aromatic positions which become deuteriated,‡ since otherwise an additional deuterium would have been introduced at a non-aromatic position.[76,77] This conclusion is in agreement with the observation that voacamine only possesses six aromatic protons and is converted to a d_6-derivative on heating in methanolic DCl.

[73] H.-G. Boit, Ergebnisse der Alkaloid-Chemie bis 1960, Akademie-Verlag, Berlin, 1961, p. 653; J. E. Saxton: 'The Indole Alkaloids,' in: 'The Alkaloids,' ed. R. H. F. Manske, Vol. VII, 1960, p. 139; W. I. Taylor, 'The Iboga and Voacanga Alkaloids,' in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII, 1965, p. 229.

[74] G. Büchi, *Pure Appl. Chem.*, 1964, **9**, 21.

[75] W. Winkler, *Naturwiss.*, 1961, **48**, 694.

[76] G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, 1963, **85**, 1893.

[77] G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, 1964, **86**, 4632.

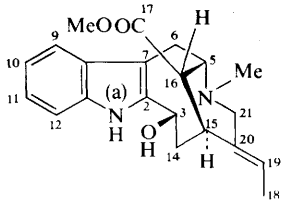
* An n.m.r. study of the secamines and model compounds has since shown that structures (127a) and (138a), rather than (127b) and (138b), are correct for secamine and presecamine respectively. In addition, the presecamines have been shown to be naturally occurring compounds. The same is probably true of the secamines (personal communication from G. A. Cordell, G. N. Smith, and G. F. Smith).

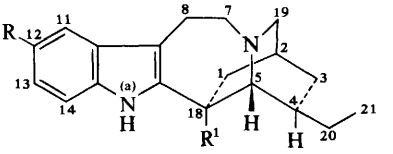
† The published work in this field up to 1961 has been discussed in detail in review articles.[73] This work is therefore not specifically cited in the text.

‡ It should be noted that the reaction path discussed in the ref. 76 would very probably lead to the introduction of a deuterium at position 4 of the voacangine (142).

Voacamine readily undergoes mono-demethoxycarbonylation in which the methoxycarbonyl group of the voacangine 'half' (α-indolylacetic acid derivative) is lost.

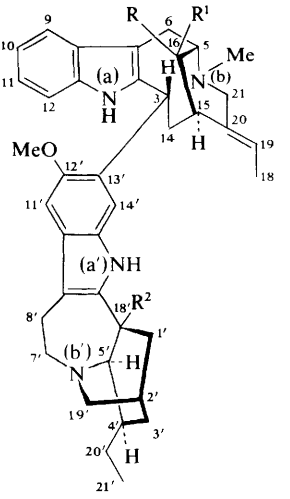
Sodium methoxide catalyses the conversion of voacamine (141) to epivoacamine (143). The epi-derivative shows a singlet n.m.r. signal at 3.57 p.p.m. corresponding to two COOMe groupings; in the spectrum of voacamine itself separate singlets at 3.61 and 2.44 p.p.m. are apparent. This behaviour is characteristic of vobasine (139) (δ of the methoxycarbonyl group which is shielded by the indole system = 2.63 p.p.m.) and its 16-epimer (δ = 3.53 p.p.m.).[78] The inference that voacamine





(139) 3-keto; Vobasine
(144) Vobasinol
(147) 19,20-dihydro, 20α-H; Dregaminol

(140) R = H; R^1 = COOMe; Coronaridine
(142) R = OMe; R^1 = COOMe; Voacangine
(160) R = OMe; R^1 = H; Ibogaine



(141) R = R^2 = COOMe; R^1 = H; Voacamine
(143) R = H; R^1 = R^2 = COOMe; Epivoacamine
(146) 19,20-dihydro, 20α-H
(158) R = COOMe; R^1 = R^2 = H; Demethoxycarbonylvoacamine
(159) $N_{(b)}$-oxide

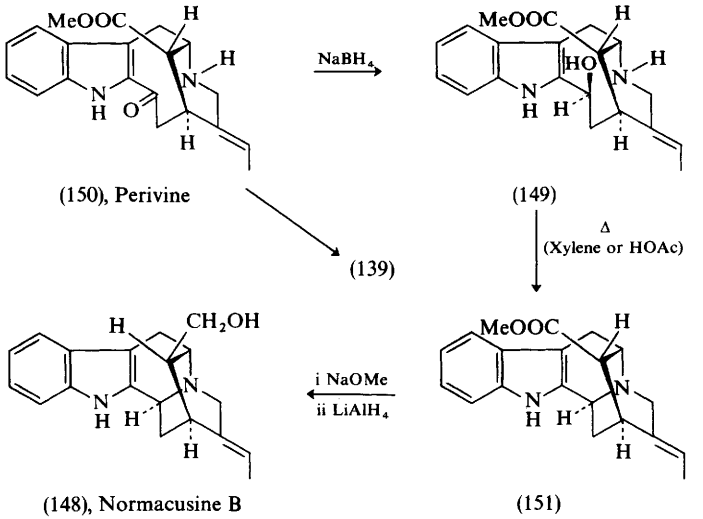
[78] U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta*, 1963, **46**, 2186.

contains a vobasine-like component is supported by the fact that Hofmann degradation of the $N_{(b)}$-quaternary methyl salt of voacamine proceeds in an analogous manner to that of the corresponding vobasine salt.[77]

Since the voacangine component of voacamine (141) is linked by a benzene ring carbon, the vobasine part must be linked through a centre which was potentially electrophilic in the monomer. Since all vobasine alkaloids are oxygenated at C(3) it is likely that this is the centre which participates in the Friedel–Crafts-like 'dimerisation' process. In fact, heating of vobasinol (144) and voacangine (142) in dilute hydrochloric acid results in ready condensation to voacamine (141).*[77,80] The condensation proceeds, at least in part, *via* an intermediate, voacamidine (145), which is a naturally occurring isomer of voacamine.[77] Voacamidine, which on heating in hydrochloric acid is converted to voacamine, is therefore the thermodynamically less stable isomer. Voacangine (142) as a 5-methoxyindole derivative can undergo electrophilic substitution at position 4 or 6. Since position 4 is substituted in voacamidine (145), only position 6 is left as a point of linkage for voacamine, thus leading to structure (141); a singlet at 6.72 p.p.m. in the n.m.r. spectrum of voacamine is in agreement.

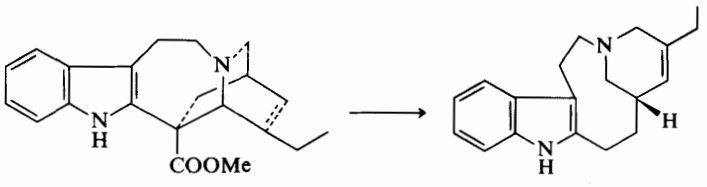
A particularly facile synthesis is that of 19,20-dihydrovoacamine (146) from dregaminol (147) and voacangine (142).[77]

The absolute stereochemistry of vobasinol (144) has been established by chemical correlation with normacusine B (148). Of the conversions associated

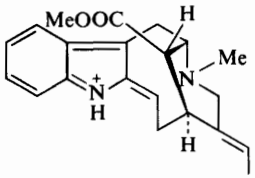


[79] U. Renner, private communication.
[80] U. Renner and H. Fritz, *Tetrahedron Letters*, 1964, 283.

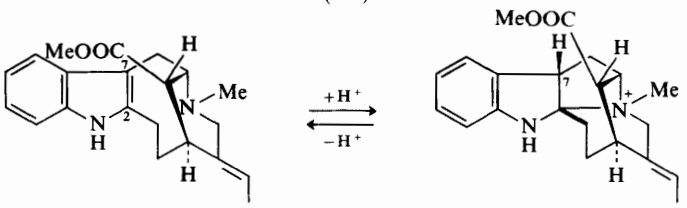
* In one case[80] the synthetic product was identical with the natural alkaloid apart from a difference in the Keller colour reaction. It is likely that an impurity in the natural product, which could be destroyed by boiling in HCl, was responsible for this difference.[79]



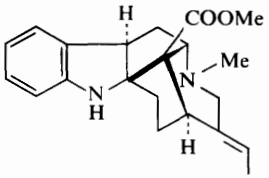
(152) (153)



(154)



(155) (156)



(157)

with this correlation, one, the cyclisation of perivinol (149) [from perivine (150)] to the pentacyclic (151) when it is heated in xylene or glacial acetic acid, is of particular interest.[77]

The second component of voacamine, voacangine (142), has been unambiguously correlated with catharanthine (152). The latter is converted by reductive demethoxycarbonylation to cleavamine (153), whose absolute stereochemistry has been determined by *X*-ray analysis (*cf.* ref. 77).

In the condensation to voacamine (141) the voacangine (142) molecule presumably attacks the immonium species (154). From consideration of models it appears probable that the nucleophile will bond to C(3) of (154) from the α-face, resulting in the 3β-H configuration for voacamine (141).[77] The different n.m.r. absorption ($\Delta\delta$ = 0.5 p.p.m.) of the C(3)-hydrogens in voacamine (141) and 16-epivoacamine

(143) indicates, in addition, that the hydrogen concerned is *syn*-orientated with respect to the methoxycarbonyl group at C(16), *i.e.* it is β. A further argument may be invoked. 3-Desoxovobasine (155), obtained by reductive cleavage of voacamine, exhibits in acidic medium the u.v. spectrum of an indoline rather than an indole.[79] Protonation thus occurs at C(7) with concomitant cyclisation to (156) (see refs. 81 and 82). The u.v. spectrum of voacamine (141) is virtually unchanged on acidification, *i.e.* it is only significantly protonated on the two $N_{(b)}$-atoms, and ring-closure in the vobasine part does not take place. Consideration of models shows that such a cyclisation in a voacamine with an α-orientated voacangine residue at C(3) (3β-H) would lead to very strong steric interaction between the voacangine 'half' and the region of the vobasine part defined by carbons 18, 19, 20, and 21. Such interaction would not occur in the 3α-H configuration and protonation in this case should correspond to that of 3-desoxovobasine (155).*

18′-Demethoxycarbonylvoacamine (158), Voacamine-$N_{(b)}$-oxide (159), and Voacamidine (145).—Voacamine (141), on hydrolysis of the two ester functions followed by heating with methanolic hydrochloric acid, gives only 18′-demethoxycarbonyl-16-epivoacamine.[77] The actual 18′-demethoxycarbonylvoacamine (158) was obtained by partial synthesis from vobasinol (144) and ibogaine (160). It occurs naturally in *Voacanga africana* Stapf.[83]

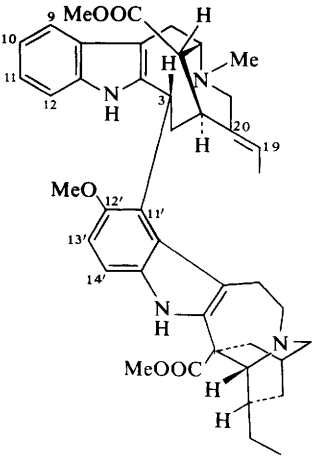
From the same plant voacamine $N_{(b)}$-oxide (159) has also been isolated. Acid-catalysed hydrolysis gives voacangine (142) and catalytic hydrogenation gives 19,20-dihydrovoacamine (146). The important n.m.r. signals of voacamine are present with the same chemical shifts in the spectrum of the $N_{(b)}$-oxide apart from the $N_{(b)}$-CH_3 singlet which is shifted downfield by 0.7 p.p.m., typical of *N*-oxide formation.[84] The alkaloid has been synthesised by condensation of voacangine (142) with vobasinol $N_{(b)}$-oxide.[84]

Voacamidine (145) has been isolated from both *V. africana* and *Conopharyngia durissima* Stapf. On acid treatment it is converted partly to voacamine (141) and partly to voacangine (142) along with the vobasinol decomposition products.[80] As mentioned (see Voacamine, p. 244) it can be partially synthesised along with voacamine (141) by acid-catalysed condensation of voacangine (142) and vobasinol (144) as the kinetically-controlled product (see refs. 77 and 85). In contrast to that of voacamine (141) its n.m.r. spectrum shows two doublets at 7.05 and 6.70 p.p.m., due to two *ortho*-coupled aromatic protons for which only the voacangine part can be responsible. Condensation of 9,10,11,12-tetradeuteriodregaminol ($^2H_4$-147) with voacangine (142) gives 19,20-dihydro-20α-[$^2H_4$]voacamidine† whose n.m.r. spectrum, as expected, shows two doublets at 7.18 and

[81] H. Bickel, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1955, **38**, 649.
[82] M. Hesse, W. v. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W. I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1964, **47**, 878.
[83] D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, 1965, **87**, 5447.
[84] F. Puisieux, J.-P. Devissaguet, C. Miet, and J. Poisson, *Bull. Soc. chim. France*, 1967, 251.
[85] S. A. Monti, W. O. Johnson, and D. H. White, *Tetrahedron Letters*, 1966, 4459.

* When heated in acid (155) cyclises to (157).[79]
† This product has not been formally identified with authentic dihydrovoacamidine.

6.88 p.p.m. Consideration of the structure of voacamidine (145)* shows that the aromatic[64] methoxy-group of the voacangine part must be strongly shielded by the indole system of the vobasinol 'half' (δ = 3.08 p.p.m.).



(145), Voacamidine

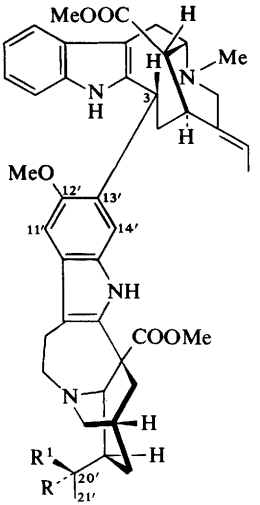
Voacorine (161) and 20′-Epivoacorine (162).—The first-named bisindole alkaloid is encountered in a number of *Conopharyngia* and *Voacanga* species, its C(20′)-epimer in *Voacanga bracteata* Stapf.[86] The n.m.r. spectrum of voacorine (161) is extremely similar to that of voacamine (141). In particular, the signal of the aromatic methoxy-group is at the 'normal' position. The principal difference results from the presence of a C(20′)-hydroxy-group which gives rise to a methyl doublet at 0.95 p.p.m.[87] The alkaloid can be split by acid hydrolysis to give voacristine (163)† (= voacangarine)[89] and synthesised *via* acid-catalysed condensation of the latter with vobasinol (144); structure (161) therefore follows.[77]

From spectroscopic data and the formation on hydrolysis of 20-epivoacristine (164), structure (162) follows for 20′-epivoacorine.[88]

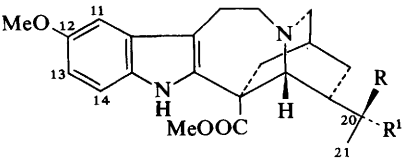
Gabunine (165), Conodurine (166), and Conoduramine (167).—Gabunine (165), from the Apocynaceae *Gabunia odoratissima* Stapf.[90] contains, in contrast to the previously described bisindole alkaloids of this group, no *N*-methyl function.

[86] F. Puisieux, M. B. Patel, J. M. Rowson, and J. Poisson, *Ann. pharm. franc.*, 1965, **23**, 33.
[87] H. Budzikiewicz, C. Djerassi, F. Puisieux, F. Percheron, and J. Poisson, *Bull. Soc. chim. France*, 1963, 1899.
[88] J. Poisson, F. Puisieux, C. Miet, and M. B. Patel, *Bull. Soc. chim. France*, 1965, 3549.
[89] W. Winkler, *Arch. Pharm.*, 1962, **295**, 895.
[90] M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, R. F. Raffauf, and J. L. Beal, *Tetrahedron Letters*, 1965, 931.

* The stereochemistry at C(3) presumably corresponds to that of voacamine (141).
† The absolute configuration of voacristine, apart from that at C(20), has been established by correlation. That of C(20) has been proposed on the basis of molecular rotational differences.[88]



(161) R = OH; R^1 = H; Voacorine
(162) R = H; R^1 = OH; 20′-Epivoacorine



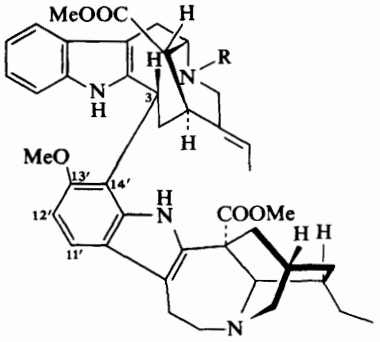
(163) R = OH; R^1 = H; Voacristine
(164) R = H; R^1 = OH; 20′-Epivoacristine

Mild methylating conditions (formaldehyde and Pd–H_2) convert gabunine (165) into conodurine (166).[90] Since gabunine and conodurine show almost identical rotations, they are assigned the same absolute stereochemistry. As well as co-occurring with gabunine in *G. odoratissima*, conodurine (166) and its isomer conoduramine (167) have also been found in *Conopharyngia odoratissima* Stapf. Conodurine (166) on cleavage yields isovoacangine (168)* and can be synthesised by warming an acidic solution of the latter and vobasinol (144).[80] As expected, the second possible isomer, identical with conoduramine (167), is also formed. The points of linkage of the two components of each 'dimer' follow from their n.m.r. spectra: conodurine possesses two *ortho*-related aromatic protons in the voacangine component, conoduramine has two which are *para*-related. Under equilibrium control the synthesis yields conodurine (166) and conoduramine (167) in the ratio 1 : 2 which is in accord with the less important steric interactions between the two 'halves' in (167).

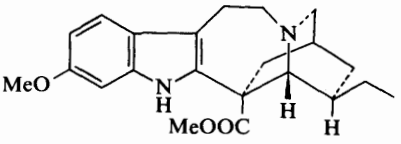
Mass Spectral Behaviour[77,83,84,87,88,91,92].—The mass spectra of voacamine (141) and its relatives show characteristic groups of peaks. At higher mass numbers are signals due to the loss of methoxycarbonyl and methyl groups. The region corresponding to 'monomers' is practically empty, but between *m/e* 100 and 200 typical fragment ion peaks for the two 'halves' are observed, namely

[91] Ref. 5, p. 72.
[92] K. Biemann, *Fortschr. Chem. org. Naturstoffe*, 1966, **24**, 1.

* Isovoacangine and voacangine (142) have very similar rotations and thus probably have the same absolute stereochemistry, *i.e.* that depicted in (142) and (168).

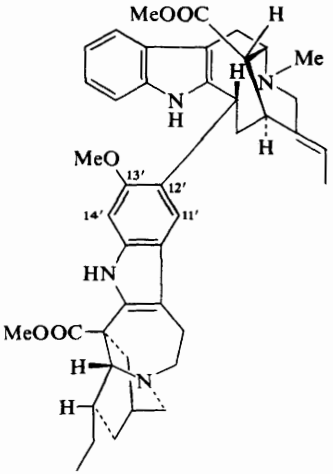


(165) R = H; Gabunine
(166) R = Me; Conodurine



(168), Isovoacangine

(166) ⇄



(167), Conoduramine

m/e 122, 124, 136, and 148 and *m/e* 122, 180, 181, 182, and 194. These groups are observed in the spectra of voacangine (142) and vobasinol (144) respectively. The absence of the typical methoxyindole peaks at *m/e* 160 and 174 and the presence of weak *m/e* 130 and 144 peaks leads to the conclusion that a coupling of the type vobasinol (aliphatic part)–voacangine (aromatic part) is present. The mass spectrum of voacamine (141) shows, in addition to the molecular ion ($M^+ = 704$), a peak at *m/e* 718; the ion corresponding to this peak arises from a thermal transmethylation process in the mass spectrometer (see Section 17, p. 322).[92,93]

[93] M. Hesse, *Fortschr. Chem. Forsch.*, 1967, **8**, 608.

10 Alkaloids of the Vinblastine Type*

In 1959 a series of bisindole alkaloids were isolated from *Vinca rosea* L. (*Catharanthus roseus* G. Don). Of signal importance have been vinblastine (169) (= vincaleukoblastine) and vincristine (170) (= leurocristine), both of which show anti-tumour activity[96–98] (see Section 18, p. 333). Structurally clarified also are leurosidine (= vinrosidine), leurosine, pleurosine, and 'isoleurosine', while only one 'half' of catharine is known.

Vinblastine (169) and Vincristine (170).—The alkaloids each possess two individual chromophores, an indole and a 6-methoxyindoline in vinblastine, an indole and an *N*-formyl-6-methoxyindoline in vincristine. The indoline moiety is part of an aspidospermine-type skeleton and the indole part of a 5,18-*chano*-ibogamine skeleton. The mode of linkage of the two units (aromatic position of the indoline to the α-indolylic position of the indole) corresponds to that present in the voacamine group (see Section 9).

An important landmark in the elucidation of the structure of vinblastine (169), $C_{46}H_{58}O_9N_4$, was the discovery that the i.r. spectrum was largely superimposable on the addition spectrum of two monomeric *Vinca* alkaloids, namely vindoline (171) and catharanthine (172).[99] The structures of these two alkaloids, vindoline with a 6-methoxyindoline chromophore, catharanthine with an indole chromophore unsubstituted on nitrogen, were at that time unknown.

Reduction of vinblastine (169) or vincristine (170), $C_{46}H_{56}O_{10}N_4$, with lithium aluminium hydride gives the same pentahydroxy-derivative, $C_{42}H_{56}O_6N_4$, thus correlating the two alkaloids with each other.[100]

From i.r. and n.m.r. evidence each 'dimer' possesses two carbomethoxy-, one aromatic *O*-methyl-, one *O*-acetyl-, one indolic NH-, and two acetylatable tertiary hydroxy-groups. As described in the introduction, the difference between the two lies only in the substitution on the indoline nitrogen atom ($-CH_3$ and $-CHO$).[100]

Reductive cleavage (conc. HCl–$SnCl_2$–Sn) of the 'dimers' leads to one and the same indolic base, velbanamine (173, $C_{19}H_{26}ON_2$), and a different indoline, desacetyl-vindoline (174) from vinblastine and des-$N_{(a)}$-methyldesacetylvindoline (175) from vincristine.[100]

It has been possible to elucidate the constitution (169) for vinblastine from

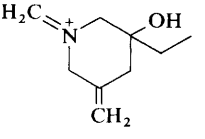
[94] W. I. Taylor, 'The Vinca Alkaloids,' in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII, 1965, 269.
[95] N. Neuss, *Bull. Soc. chim. France*, 1963, 1509.
[96] G. H. Svoboda, N. Neuss, and M. Gorman, *J. Amer. Pharm. Assoc., Sci. Edn.*, 1959, **48**, 659.
[97] N. Neuss, M. Gorman, G. H. Svoboda, G. Maciak, and C. T. Beer, *J. Amer. Chem. Soc.*, 1959, **81**, 4754.
[98] G. H. Svoboda, I. S. Johnson, M. Gorman, and N. Neuss, *J. Pharm. Sci.*, 1962, **51**, 707.
[99] M. Gorman, N. Neuss, and G. H. Svoboda, *J. Amer. Chem. Soc.*, 1959, **81**, 4745.
[100] N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *J. Amer. Chem. Soc.*, 1962, **84**, 1509.

* The work appearing up to 1962/63 has been reviewed, see refs. 74, 94 and 95.

chemical and spectroscopic data.[101] The relative and absolute configuration has been determined from an *X*-ray analysis of vincristine-$N_{(b)}$-methiodide.[102]

The indolic cleavage product velbanamine (173) shows similarities to the so-called cleavamine (176, $C_{19}H_{24}N_2$, absolute configuration[103]) which is formed on acid-catalysed reduction of catharanthine (172). Velbanamine can thus be concluded to be a dihydro-hydroxy-derivative of (176) with a tertiary hydroxy-group. Owing to the earlier determination of an incorrect molecular formula (2 hydrogens less) for vinblastine and vincristine it was assumed that the indole portion of these 'dimers' represented a dihydro-dihydroxy-catharanthine. Establishment of the correct molecular formulae made the idea of a pentacyclic second 'half' untenable. The n.m.r. spectra of (169) and (170) show that only six aromatic protons can be present and that the vindoline component is substituted at C(15).[100]

The constitution of velbanamine (173), particularly the location of the hydroxy-function, follows from a closer analysis of its mass spectral fragmentation. The fragment ion corresponding to the base peak has been assigned structure *e*.



e

(*m/e* 154)

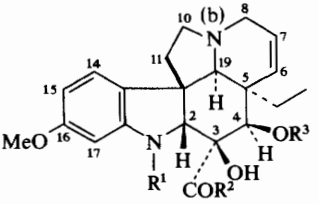
Along with velbanamine (173) the reductive acid cleavage of vinblastine and vincristine gives some cleavamine (176). This latter is presumably formed by acid-catalysed elimination of water from (173). It therefore follows that in velbanamine (173) and cleavamine (176) centre 2 has the same chirality.[104] The absolute configuration of centre 4 was determined from the previously mentioned *X*-ray analysis of vincristine methiodide, as well as by the reductive acid cleavage of the hydrazide (177) to velbanamine (see later).

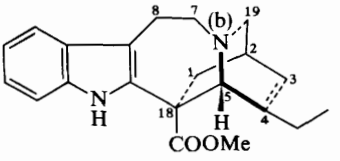
The actual structure of the 'indolic half' in vinblastine (169) itself and the nature of its linkage with C(15) of the 'vindoline half' follows from the following experiments.[105] Prolonged boiling of vinblastine with hydrazine gives de-methoxycarbonyl-desacetylvinblastine monohydrazide (177, $C_{41}H_{54}O_5N_6$) which on reductive acid cleavage yields desacetylvindoline hydrazide (178) and velbanamine (173). Reductive cleavage of vinblastine (169) in a deuteriating medium leads to [$^2H_6$]velbanamine ($^2H_6$-173) in which four deuteriums are attached to the benzene ring and the remaining two to C(18) or one each to C(18)

[101] M. Gorman, N. Neuss, and K. Biemann, *J. Amer. Chem. Soc.*, 1962, **84**, 1058.
[102] J. W. Moncrief and W. N. Lipscomb, *J. Amer. Chem. Soc.*, 1965, **87**, 4963.
[103] J. P. Kutney, R. T. Brown, and E. Piers, *Canad. J. Chem.*, 1966, **44**, 637.
[104] J. P. Kutney, private communication on experiments of Dr. N. Neuss.
[105] N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Amer. Chem. Soc.*, 1964, **86**, 1440.

and C(8) (mass spectral evidence, fragment *e* unchanged). C(8) or C(18) must therefore be a terminus for the coupling.

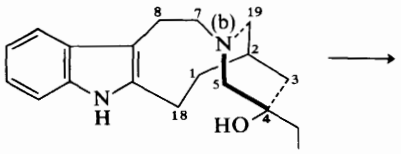
Acid-catalysed cleavage in the *absence* of reducing agent gives the amino-acid (179); this can be converted to the ester (180), which with $SnCl_2$ in $DCl–D_2O$ again gives [$^2H_6$]velbanamine ($^2H_6$-173) in which C(18) must carry two deuterium atoms;* the formation of ($^2H_6$-173) from both (169) and (180) excludes C(8′) as a linkage position and leaves C(18′) as the only possibility. The complete structures (169) and (170) follow for vinblastine and vincristine respectively.[105,†]



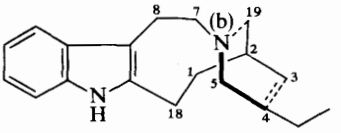


(171) R^1 = Me; R^2 = OMe; R^3 = COMe; Vindoline
(174) R^1 = Me; R^2 = OMe; R^3 = H
(175) R^1 = H; R^2 = OMe; R^3 = H
(178) R^1 = Me; R^2 = $NHNH_2$; R^3 = H

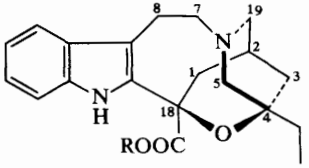
(172), Catharanthine



(173), Velbanamine



(176), Cleavamine

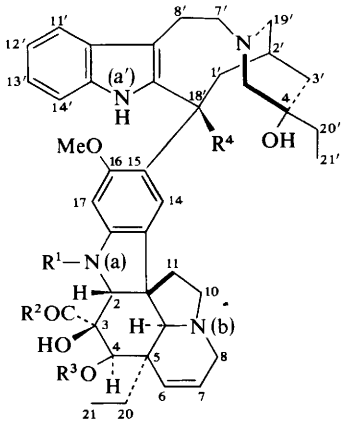


(179) R = H
(180) R = Me

The structures thus elucidated have been confirmed by *X*-ray analysis of vincristine methiodide;[102] this led also to the absolute stereochemistry of the alkaloids which is depicted in (169) and (170). As far as is known, partial syntheses of these 'dimeric' alkaloids have not been achieved (see ref. 74).

* Under the experimental conditions employed 1,2,3,4-tetrahydrocarbazoles exchange, as well as the aromatic protons, only those at C(1) and C(4).

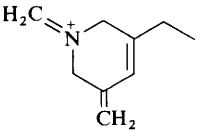
† It is probable that the C(4′)-hydroxy-group of vinblastine, which is ideally situated as a neighbouring group, plays a direct part in the hydrolysis; after protonation of C(15) the vindoline residue is expelled with inversion of C(18′) to give the ether (179)/(180). Reductive opening of the ether ring then follows.



(169) R^1 = Me; R^2 = OMe; R^3 = COMe; R^4 = CO_2Me; Vinblastine
(170) R^1 = CHO; R^2 = OMe; R^3 = COMe; R^4 = CO_2Me; Vincristine
(177) R^1 = Me; R^2 = $NHNH_2$, R^3 = R^4 = H

Leurosidine (181).—The third bisindole alkaloid of this group from *Vinca rosea* L. to be investigated was leurosidine (181), $C_{46}H_{58}O_9N_4$ (= vinrosidine), an isomer of vinblastine (169).

Reductive cleavage of the alkaloid ($SnCl_2$–Sn–HCl) gives desacetylvindoline (174), cleavamine (176), and small amounts of vinrosamine (182). Similar treatment of leurosidine hydrazide gives (176) and (182) along with desacetylvindoline hydrazide (178). Vinrosamine (182) is isomeric with velbanamine (173). It readily gives an *O*-acetyl derivative and can be oxidised to a ketone. Since leurosidine (181) shows pK'_a values (in 33% dimethylformamide) of 5.4 for $N_{(b)}$ and 8.8 for $N_{(b')}$ compared with 5.4 and 7.4 respectively for vinblastine (169), the secondary hydroxy-group in the vinrosamine component cannot be part of a carbinolamine ether system. In the mass spectrum a peak corresponding to the ion *f* is observed.

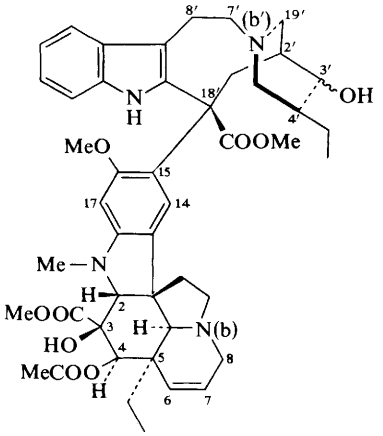


f
(*m/e* 136)

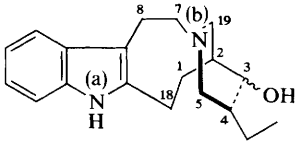
Under the assumption that leurosidine (181) and vinrosamine (182) each possess an ethyl group,* and that the vindoline component is linked as in vinblastine (169),* the formulae (181) and (182) follow for leurosidine and vinrosamine respectively.

[106] N. Neuss, L. L. Huckstep, and N. J. Cone, *Tetrahedron Letters*, 1967, 811.

* In ref. 106 and earlier publications no details concerning this point are given.



(181), Leurosidine



(182), Vinrosamine

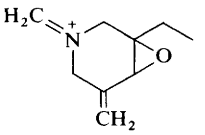
Leurosine (183), Pleurosine (184) (= leurosine $N_{(b')}$-oxide), and 'Isoleurosine' (185) (= 4′-desoxyvinblastine).—Leurosine (183, $C_{46}H_{56}O_9N_4$), which contains an ether function, on heating with Raney nickel gives the so-called isoleurosine (185, $C_{46}H_{58}O_8N_4$, = 4′-desoxyvinblastine), which occurs naturally, together with 4′-desoxy-4′-epivinblastine (186). Cleavage with $SnCl_2$–Sn–HCl of the 18′-demethoxycarbonyl-4-desacetyl hydrazides of the bases (185) and (186) gives 4β-*H*-dihydrocleavamine (187)* and 4α-*H*-dihydrocleavamine (188)* respectively, together in both cases with desacetylvindoline hydrazide (178).[107–109]

From n.m.r. data it follows that the benzene ring of the vindoline part of leurosine and its derivatives has the same substitution pattern as in vinblastine (169). In the mass spectrum of leurosine a peak at *m/e* 152 ($C_9H_{14}ON$) of probable structure g is observed, which means that the oxygen function in the upper half must be in ring D, since the alkaloid possesses a *C*-ethyl group.† Leurosine cannot be acetylated (acetic anhydride–pyridine; keten), a fact which, together with the i.r. spectrum, speaks for the ether nature of the oxygen function in the upper half. The conversion of the 'dimer' into the two desoxy-vinblastines [(185)

[107] N. Neuss, M. Gorman, N. J. Cone, and L. L. Huckstep, *Tetrahedron Letters*, 1968, 783.
[108] J. P. Kutney, R. T. Brown, and E. Piers, *Canad. J. Chem.*, 1965, **43**, 1545.
[109] D. J. Abraham and N. R. Farnsworth, *J. Pharm. Sci.*, 1969, **58**, 694.
[110] J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. and Ind.*, 1963, 648; J. P. Kutney and E. Piers, *J. Amer. Chem. Soc.*, 1964, **86**, 953; A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Letters*, 1965, 637.

* 4β-*H*-Dihydrocleavamine (187) = 4α-ethyldihydrocleavamine = 4α-dihydrocleavamine; 4α-*H*-dihydrocleavamine (188) = 4β-dihydrocleavamine which was previously termed 'dihydro-cleavamine' (see refs. 108 and 110).

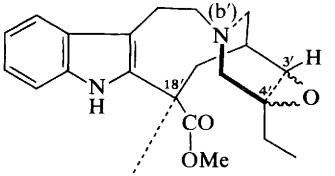
† Not expressly stated in the work on leurosine.



g
(*m/e* 152)

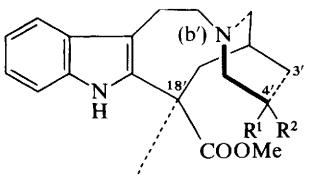
and (186)] with Raney nickel suggests an epoxide grouping.* The pK'_a values of leurosine, 5.5 for $N_{(b)}$ and 7.5 for $N_{(b')}$, eliminate C-atoms α to $N_{(b')}$ as ether bridge positions. A doublet in its n.m.r. spectrum at 3.1 p.p.m. [$J = 4$ Hz; C(3′)-H] is reconcilable with the epoxide grouping.

An attempt has been made to condense the chlorindolenine of 4α-*H*-dihydrocleavamine (188) with desacetylvindoline hydrazide (178) in dilute acid to give 18′-demethoxycarbonyl-4-desacetyl-4′-desoxy-4′-epivinblastine hydrazide (190). Instead the C(18′)-epimer (191) is formed [low-field doublet of the C(18′)-H at



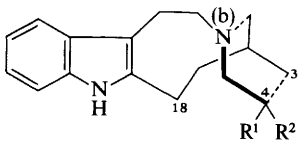
C(15)-Vindolinyl

(183), Leurosine
(184), $N_{(b')}$-oxide

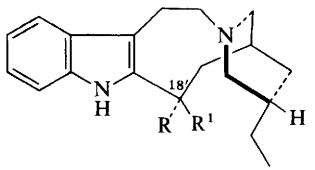


C(15)-Vindolinyl

(185) $R^1 = H$; $R^2 = Et$; Isoleurosine
(186) $R^1 = Et$; $R^2 = H$

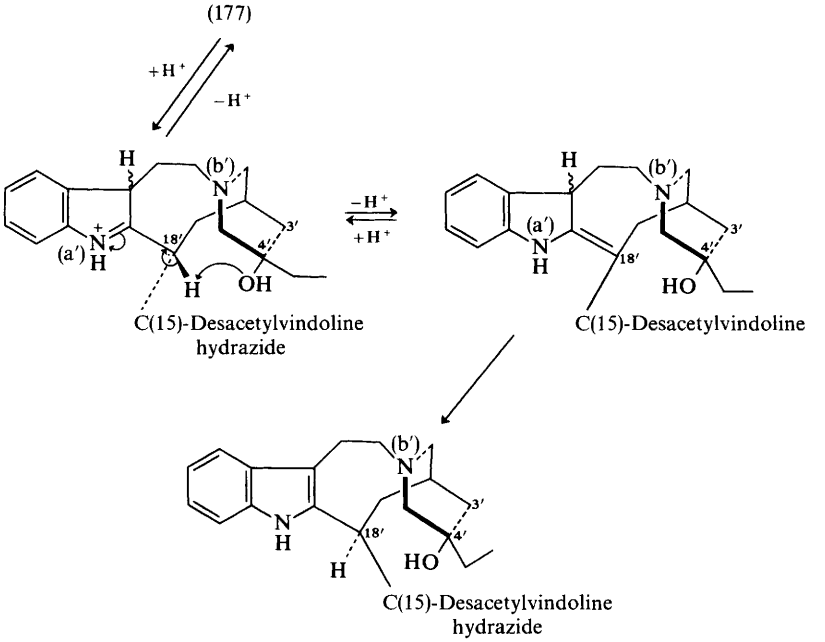


(187), $R^1 = H$; $R^2 = Et$
(188), $R^1 = Et$; $R^2 = H$



(190) R = C(15)-Desacetylvindoline hydrazide; $R^1 = H$
(191) R = H; R^1 = C(15)-Desacetylvindoline hydrazide

* Surprisingly the intermediate product of Raney nickel reduction, the carbinol, is not encountered and is obviously further reduced. This suggests a tertiary carbinol as the intermediate.



(189)

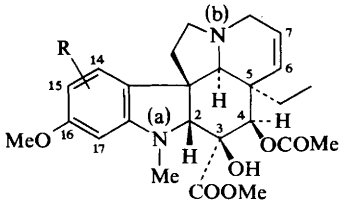
Scheme 10

4.5 p.p.m. (J = 10 Hz); in (190) the corresponding signal lies at higher field]. While the compounds of the 4′-desoxy-series are stable to hot 1.5 % hydrochloric acid, the 18′-demethoxycarbonyl-4-desacetylvinblastine hydrazide (177) is converted to its C(18′)-epimer (189) [n.m.r. doublet at 4.6 p.p.m. (J = 10 Hz)]. Clearly the presence of the 4′-hydroxy-group, presumably acting as an internal base, is necessary to effect the C(18′)-epimerisation of vinblastine derivatives. In the C(18′)-epimers it is sterically impossible for the hydroxy-group to function in this manner, *i.e.* the epimerisation is kinetically controlled (see Scheme 10). The desoxy-bases (185) and (186), owing to the lack of the hydroxy-function, cannot be epimerised, at least not in 1.5 % hydrochloric acid.

The proposed mechanism of epimerisation would mean that the normal 18′-demethoxycarbonyl-compounds possess the 18′β-H configuration; the epimeric bases (189) and (191) with the 18′α-H configuration are characterised, as described, by a low-field doublet in the n.m.r. spectrum.

The 'dimer' pleurosine (184, $C_{46}H_{56}O_{10}N_4$) shows pK'_a values of 5.5 (vindoline part) and 4.4 (cleavamine-like part). Mild treatment with zinc in acetic acid converts this alkaloid to leurosine (183). Pleurosine is therefore leurosine $N_{(b')}$-oxide.[107]

Catharine (192).—Little is known concerning the alkaloid catharine, for which the part structure (192) has been proposed.[111,*]



(192), partial structure of catharine
R = $C_{21}H_{23}O_4N_2$

Mass Spectra.—The mass spectral behaviour of the vinblastine alkaloids is similar to that of voacamine and its relatives. Transmethylation reactions are observed, *e.g.* for vinblastine (169) (M^+ = 810) peaks occur at *m/e* 824 and 838 this being one of the major reasons for the utilisation of hydrazide derivatives. The nature of the two structurally different components can be recognised from characteristic fragment ions in the low-mass region.[92,105,109,112]

11 The Pycnanthine Group

This group is to date comprised of three closely related bases, (+)-pycnanthine (193), pleiomutinine (194), and (+)-pycnanthinine (195). Pycnanthine (193) has been isolated in relatively large amounts from *Pleiocarpa pycnantha* (K. Schum.) Stapf. *var. pycnantha* M. Pichon,[113] pycnanthinine (195) being a very minor alkaloid of the same plant.[114] Pleiomutinine (194) has been isolated in very small amounts from *Pleiocarpa mutica* Benth.[115] The structures of pycnanthinine and pleiomutinine are largely based on the constitution determined for pycnanthine.

Pycnanthine (193) and Pleiomutinine (194).[113]—Pycnanthine has the molecular formula $C_{40}H_{44}O_2N_4$. Its u.v. spectrum is not a summation of two of the chromophores commonly encountered in the indole alkaloid field. The mode of linkage of the two components results in interaction between their aromatic chromophores (indolines)[116] leading to a u.v. absorption unique to pycnanthine and its relatives (see Section 17, p. 319).

The alkaloid contains no OH or NH functions (i.r.; resistance to acetylation). The double ester band at 1754 and 1724 cm^{-1} in the i.r. spectrum is characteristic

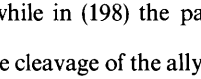
[111] D. J. Abraham, N. R. Farnsworth, R. N. Blomster, and R. E. Rhodes, *J. Pharm. Sci.*, 1967, **56**, 401.
[112] P. Bommer, W. McMurray, and K. Biemann, *J. Amer. Chem. Soc.*, 1964, **86**, 1439.
[113] A. A. Gorman, N. J. Dastoor, M. Hesse, W. v. Philipsborn, U. Renner, and H. Schmid, *Helv. Chim. Acta*, 1969, **52**, 33.
[114] A. A. Gorman and H. Schmid, *Monatsh.*, 1967, **97**, 1554.
[115] W. G. Kump and H. Schmid, *Helv. Chim. Acta*, 1961, **44**, 1503.
[116] H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1957, 1877.

* In the earlier literature a series of additional 'dimeric' alkaloids were described (see ref. 1).

of (+)-pleiocarpamine (196) and 2,7-dihydropleiocarpamine (197)[82] (see Section 12, p. 265). The n.m.r. spectrum shows the presence of the groupings –CH=CH–, =CH–CH_3, >CH–CH_3, and –$COOCH_3$.

Catalytic hydrogenation of (193) in sulphuric acid solution gives mainly (+)-6′,7′-dihydropycnanthine, which is identical with pleiomutinine (194, see ref. 113), and small amounts of 6′,7′,8′,9′-tetrahydro-8′,9′-*chano*-pycnanthine (198); the latter is the major product on hydrogenation in ethyl acetate in the presence of potassium carbonate. With methanol–acetic acid as solvent (194), (198), and the $N_{(b')}$-methyl derivative of (198), namely (199),* are obtained. All three hydrogenation products exhibit the same u.v. spectrum as pycnanthine (193). Product (198) contains a secondary amine function (acetylation); (194) cannot be further hydrogenated to (198) or (199).

A detailed n.m.r. analysis of pycnanthine (193), involving extensive decoupling experiments, has led to the identification of the sequence

The ethylidene group is still present in (194) and the $\Delta^{6'}$-double bond has been reduced, while in (198) the part structure  results from Emde cleavage of the allylamine system of pycnanthine (193). Of particular importance in the structure elucidation of pycnanthine were the acid-catalysed hydrolyses (heating with mineral acid) of the alkaloid and its derivatives which are summarised in Table 1, from which it is evident that one component of pycnanthine stems from pleiocarpamine (196) and that the hydrogenations take place in the C_{19}-tuboxenine-like part. The three C_{19}-cleavage products are all indolines with an NH group.

The clarification of the structure of the C_{19}-skeleton will be discussed at the end of this Section. The difference between the normal- and iso-series concerns the configuration at C(20). It is to be noted here that tuboxenine (202)[117,118] and isotuboxenine (203) can be interconverted under acidic conditions. The thermodynamically more stable isomer in 3N-HCl is tuboxenine. Under kinetically-controlled conditions, the product obtained on acid hydrolysis of (194) is isotuboxenine (203). The stereochemistry of the 'dimer' must therefore correspond to that of (203). This has been confirmed by n.m.r. spectroscopy. The chemical shift of the methyl doublet (>$\overset{20}{C}H$–$\overset{21}{C}H_3$) in dihydropycnanthine (194) = 0.56 p.p.m.; in isotuboxenine (203) = 0.52 p.p.m.; in tuboxenine (202) = 0.81 p.p.m. The 8,9-dihydro-8,9-*chano*-isotuboxenine (204) shows the corresponding signal at 0.37 p.p.m. and forms an $N_{(a)}N_{(b)}$-diacetyl derivative (u.v., i.r., and mass spectrometric evidence).

[117] W. G. Kump, M. B. Patel, J. M. Rowson, and H. Schmid, *Helv. Chim. Acta*, 1964, **47**, 1497.

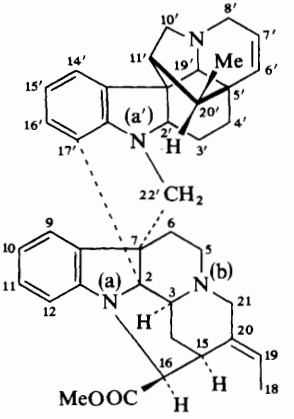
[118] C. Kump, J. Seibl, and H. Schmid, *Helv. Chim. Acta*, 1964, **57**, 358.

* The exact mode of formation of (199) is not certain.

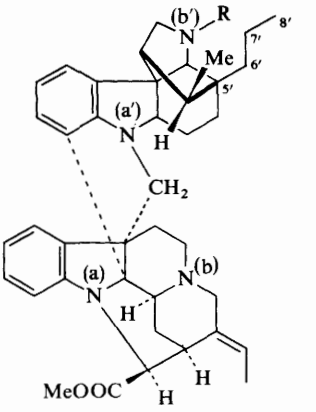
Table 1

Starting base	*Acid cleavage products*
Pycnanthine (193)	Pleiocarpamine (196) + CH_2O + 6,7-Dehydrotuboxenine (200) and 6,7-Dehydro-isotuboxenine (201)[a] ($C_{19}H_{22}N_2$)
6′,7′-Dihydropycnanthine (194) (= Pleiomutinine)	Pleiocarpamine (196) + CH_2O + Tuboxenine (202) and isotuboxenine (203) ($C_{19}H_{24}N_2$)
6′,7′,8′,9′-Tetrahydro-8′,9′-*chano*-pycnanthine (198)	Pleiocarpamine (196) + CH_2O + 8,9-Dihydro-8,9-*chano*-isotuboxenine (204)[b] ($C_{19}H_{26}N_2$)

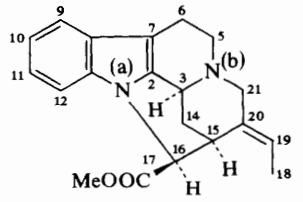
[a] This epimeric pair could not be separated by thin-layer chromatography.
[b] This product was erroneously described as 8,9-dihydro-8,9-*chano*-tuboxenine, see ref. 113.



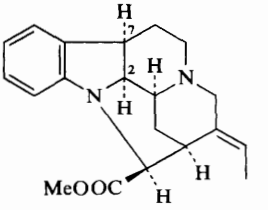
(193) Pycnanthine
(194) 6′,7′-dihydro; 6′,7′-Dihydropycnanthine = Pleiomutinine



(198) R = H
(199) R = Me



(196), Pleiocarpamine



(197), 2,7-Dihydropleiocarpamine

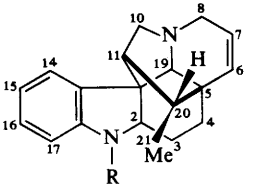
The reductive cleavage (Zn–HCl) of pycnanthine (193) results in the formation of the following products: traces of 2,7-dihydropleiocarpamine (197), isodihydropleiocarpamine (205),* an approximately 1 : 1 mixture of $N_{(a)}$-methyl-6,7-dehydrotuboxenine (206) and $N_{(a)}$-methyl-6,7-dehydro-isotuboxenine (207), together with some non-methylated products (200) and (201). The isomer mixtures could not be separated.

2,7-Dihydropleiocarpamine (197) and isodihydropleiocarpamine (205) are formed on treatment of pleiocarpamine (196) with zinc and hydrochloric acid. The formation of (205) is a result of Emde fission of the $N_{(b)}$–C(3) bond in (196) followed by addition of $N_{(b)}$ to the C(7)-protonated indole system (see ref. 81).

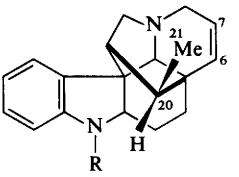
Reductive cleavage of 6′,7′-dihydropycnanthine (194) gives isodihydropleiocarpamine (205), isotuboxenine (203), and $N_{(a)}$-methylisotuboxenine (209) and traces of tuboxenine (202) and $N_{(a)}$-methyltuboxenine (208).

* The ratio 2,7-dihydropleiocarpamine: isodihydropleiocarpamine is dependent on the nature of the zinc dust employed.

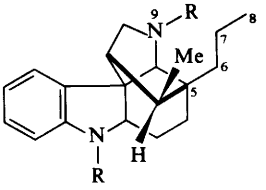
Since neither 6,7-dehydrotuboxenine (200), 6,7-dehydroisotuboxenine (201), nor tuboxenine (202) suffer any $N_{(a)}$-methylation on subjection to the reductive



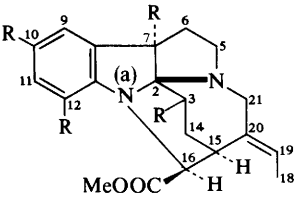
(200) R = H
(202) R = H, 6,7-dihydro; Tuboxenine
(206) R = Me
(208) R = Me, 6,7-dihydro



(201) R = H
(203) R = H, 6,7-dihydro; Isotuboxenine
(207) R = Me
(209) R = Me, 6,7-dihydro



(204) R = H



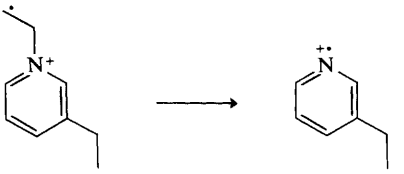
(205) R = H; Isodihydropleiocarpamine
(210) R = D

cleavage conditions in the presence of three moles of formaldehyde, it follows that the $N_{(a)}$-methyl group of the derivatives (206), (207), (208), and (209) must originate from a methylene group which is already attached to $N_{(a')}$ in the 'dimers' themselves. This methylene group is also the source of the formaldehyde formed on simple hydrolysis (Table 1).

An important observation was that pycnanthine (193) shows the characteristic n.m.r. signals of 2,7-dihydropleiocarpamine (197) rather than those of pleiocarpamine (196) itself. This concerns principally the chemical shifts and coupling constants of one of the C(21)-protons and the aromatic proton at C(12). In the spectrum of pycnanthine (193) the doublet of the proton at C(16) is identical to, but shifted 1 p.p.m. downfield relative to, that of 2,7-dihydropleiocarpamine (197). The same applies to the mass spectral fragmentation of pycnanthine (193), which shows two important peaks at *m/e* 135 (*h*) and 107 (*i*). These are characteristic of the fragmentation of 2,7-dihydropleiocarpamine (197) but are not observed in the spectrum of pleiocarpamine (196).

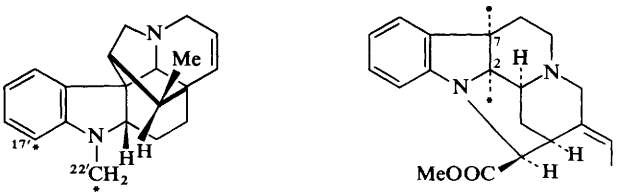
A comparison of the n.m.r. spectra of pycnanthine (193) and the monomers 2,7-dihydropleiocarpamine (197) and tuboxenine (202) shows that the 'dimer' contains seven aromatic protons. It has been possible from decoupling experiments to locate four of these on the 2,7-dihydropleiocarpamine component, and

to show that the doublet of the C(17′)-proton of the tuboxenine part, to be expected at high field, is absent.



h (*m/e* 135) *i* (*m/e* 107)

Since C(16) carries a hydrogen (n.m.r.) and fragment ion *i* includes the rest of the aliphatic carbon skeleton, only C(2) and C(7) remain as possible points of coupling in the 2,7-dihydropleiocarpamine 'half'. All the arguments so far presented lead to part structure *C* for pycnanthine.



C
partial structure of pycnanthine (193)
(stars denote linkage positions)

That coupling occurs through C(2) and C(7) is completely confirmed by reductive cleavage of pycnanthine (193) under deuteriating conditions. Along with 10,12,15′-trideuteriopycnanthine, 15,17-dideuterio-6,7-dehydrotuboxenines, and 15,17,22-trideuterio-$N_{(a)}$-methyl-6,7-dehydrotuboxenines [C(22) = $N_{(a)}$-methyl carbon atom] the 3,7,10,12-tetradeuterioisodihydropleiocarpamine (210) is obtained. Since the benzene ring protons of an indole nucleus are exchanged under acidic conditions much more slowly than the protons *ortho* and *para* to the nitrogen of an indoline nucleus, and since from the above experiment [$^2H_3$]-pycnanthine was isolated, (210) must be formed in the following ways:

(*a*) pycnanthine → [$^2H_3$]pycnanthine → [10,12-$^2H_2$]pleiocarpamine → [$^2H_4$]isodihydropleiocarpamine (210).
(*b*) pycnanthine → pleiocarpamine (196) → [3,7-$^2H_2$]isodihydropleiocarpamine → (210).

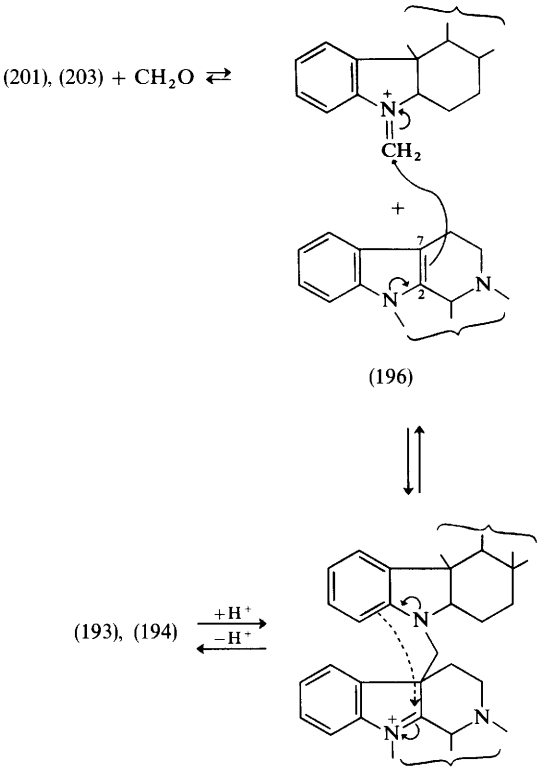
The mass spectrum of (210) is in excellent agreement with the deuterium distribution shown.

If the 2,7-dihydropleiocarpamine part were linked through a position or positions other than C(2) and C(7) more highly deuteriated forms of isodihydropleiocarpamine than (210) would result.

Partial structure *C* allows two alternative structures for pycnanthine. The strong preference for (193) is based on:

(*a*) the previously mentioned observation that the resonance of the proton at C(16) is approximately 1 p.p.m. at lower field than in the spectrum of the monomer 2,7-dihydropleiocarpamine (197); the protons of the 'dimer' otherwise absorb at positions virtually identical to those for the corresponding monomeric components. Only structure (193) can assume a conformation (lone pair on $N_{(a)}\beta$-, lone pair on $N_{(a')}$ α-orientated) in which the C(16)-hydrogen lies in the deshielding region of the benzene ring of the dehydrotuboxenine part.

(*b*) a possible biosynthesis of pycnanthine which is depicted in Scheme 11, the β-position of the indole [pleiocarpamine (196)] nucleus being more nucleophilic than the α-position. The acid-catalysed cleavage of pycnanthine clearly involves



Scheme 11

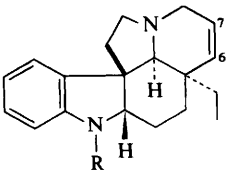
the reverse process. In the reductive cleavage process the $N_{(a)}$-methyleneimmonium intermediate is reduced in part to the $N_{(a)}$-methyl compound.

The structures shown for pycnanthine (193) and 6′,7′-dihydropycnanthine (194, = pleiomutinine) very probably represent the absolute configuration.[113]

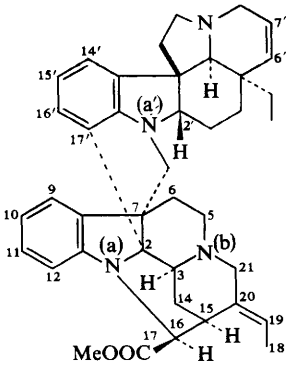
To conclude this Section, the structure of the C_{19}-skeleton will be briefly discussed: the isomeric mixture obtained from cleavage of 6′,7′-dihydropycnanthine (194) shows a mass spectrum identical to that of (+)-tuboxenine, isolated from *Pleiocarpa pycnantha*. Isotuboxenine could be isolated from the same plant[117] and has been shown to be identical by mass spectroscopy and thin-layer chromatography with the isotuboxenine obtained by reductive cleavage of 6′,7′-dihydropycnanthine (194). Under the conditions employed, tuboxenine is the thermodynamically more stable isomer. Concerning possible mechanisms of the tuboxenine–isotuboxenine interconversion see ref. 113.

(+)-Pycnanthinine (195).[114]—This alkaloid [$C_{40}H_{46}O_2N_4$, isomeric with 6′,7′-dihydropycnanthine (194)] co-occurs with (+)-pycnanthine (193) and the two bases exhibit very similar u.v. and i.r. spectra. The mass spectrum of pycnanthinine also shows the strong peaks at *m/e* 135 (*h*) and 107 (*i*).

Acid-catalysed hydrolysis of pycnanthinine (195) gives (+)-pleiocarpamine (196), (−)-6,7-dehydro-aspidospermidine (211), and formaldehyde. Reductive



(211) R = H; 6,7-Dehydroaspidospermidine
(212) R = Me



(195), Pycnanthinine

cleavage yields (211) and its $N_{(a)}$-methyl derivative (212) along with 2,7-dihydropleiocarpamine (197) and isodihydropleiocarpamine (205).

In the n.m.r. spectrum of pycnanthinine the aromatic signals are almost fully separated as four doublets and three triplets. Again the C(17')-proton is missing. The signals corresponding to protons of the 2,7-dihydropleiocarpamine unit are practically identical with those of the pycnanthine spectrum; in particular the C(16)-proton resonance occurs at 5.07 p.p.m., exactly as for pycnanthine (193). This fact, in conjunction with their identical u.v. spectra, shows that the mode of coupling in the two 'dimers' must be exactly the same. The complete structure (195) therefore follows for pycnanthinine.

12 Bisindole Alkaloids from *Alstonia* Species

Certain *Alstonia* species of the family Apocynaceae contain bisindole alkaloids of interesting construction. These are (+)-villalstonine from *Alstonia macrophylla* Wall., *A. muelleriana*, *A. somersetensis* F.M. Bailey and *A. villosa* Blume, (+)-macralstonine from *A. macrophylla* Wall., and macralstonidine from *A. macrophylla* Wall. and *A. somersetensis* F.M. Bailey. A common unit of all three 'dimers' is the monomeric indolic base macroline.

Villalstonine (213).[119,120]—The alkaloid of molecular formula $C_{41}H_{48}O_4N_4$ shows in the i.r. the 'pleiocarpamine' ester double band and an indoline band but no OH or NH absorption. On standing in cold 70 % perchloric acid it gives (+)-pleiocarpamine (196), the other 'half' being destroyed. On controlled treatment of villalstonine (213) with trifluoracetic acid–trifluoracetic anhydride a mixture of two products, both isomeric with the alkaloid, is formed; these are villamine (214), the main component, and villoine, which has not been further investigated. Villamine (214) is a key product for the degradation of villalstonine, since it can be converted back to the latter on heating in 1N-HCl. Villamine (214) contains a hydroxy-group which can be acetylated and an enol ether function (i.r. 1682 cm^{-1}).

The mass spectrum of villamine is extremely informative. Apart from the molecular ion ($M^+ = 660$) the spectrum is virtually a summation of the mass spectra of pleiocarpamine (196, $C_{20}H_{22}O_2N_2$, $M^+ = 322$) and the base macroline (215, $C_{21}H_{26}O_2N_2$, $M^+ = 338$). This suggests that in the mass spectrometer villamine (214) is breaking down to pleiocarpamine and macroline. Thermolysis at 250 °C in high vacuum does in fact split villamine into these two bases. Separation is facilitated by brief treatment with methyl iodide which converts pleiocarpamine (196) to the corresponding methiodide while macroline remains unchanged. Simple partition between water and chloroform then achieves separation. The structure of macroline (215) will be discussed at the end of this

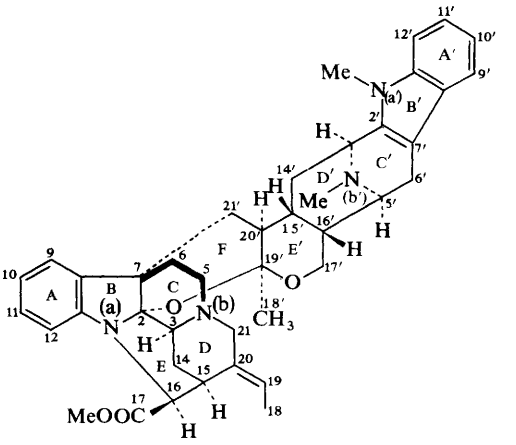
[119] M. Hesse, H. Hürzeler, C. W. Gemenden, B. S. Joshi, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, 1965, **48**, 689.

[120] M. Hesse, F. Bodmer, C. W. Gemenden, B. S. Joshi, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 1173.

section. *O*-Acetylvillamine (216) on pyrolysis gives pleiocarpamine (196) and *O*-acetylmacroline (217).

The following observations are important for the elucidation of part structure *D* for villamine:

(*a*) The u.v. spectrum of villamine is the summation of an indoline and an indole chromophore.



(213), Villalstonine

(*b*) The $\alpha\beta$-unsaturated ketone of macroline (215) is absent from villamine (214) (no i.r. C=O absorption; no vinyl proton signals in the n.m.r.). In its place is the previously mentioned enol ether grouping.

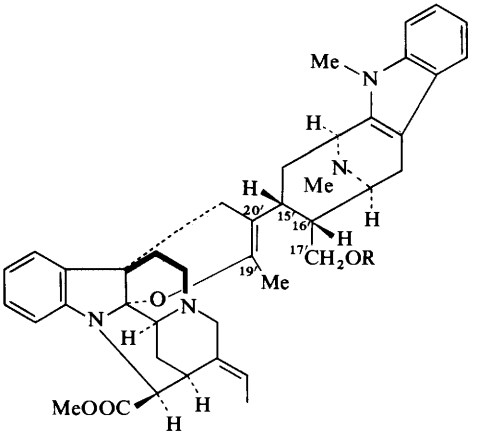
(*c*) Villamine (214) shows signals in the n.m.r. which are characteristic of 2,7-dihydropleiocarpamine (197) (see the pycnanthine group, Section 11). In addition, the methyl singlet of an *N*-methylindole appears at 3.64 p.p.m. (the corresponding absorption of *N*-methylindolines occurs at approximately 2.8 p.p.m.).

These data show that villamine is a 2,7-dihydropleiocarpamine derivative. The thermal cleavage to pleiocarpamine (196) and macroline (215) is considered to be of the retro-Diels–Alder type.

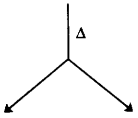
Villalstonine (213) contains no hydroxy-groups and no enol ether grouping. It must therefore possess a six-membered ether ring, formed by hydroxy-group addition to the enol ether double bond of villamine (214) {supported by a methyl singlet [C(18′)H_3 at 1.31 p.p.m.]}. *E* therefore represents the part structure of villalstonine itself.

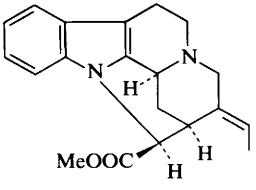
Thus, two alternative pairs of structures are possible for villalstonine and villamine; the following arguments allow a distinction to be made in favour of (213) and (214).

(*a*) Biogenetic considerations: probable precursors would be pleiocarpamine (196) and macroline (215) which has not yet as such been encountered in *Alstonia*

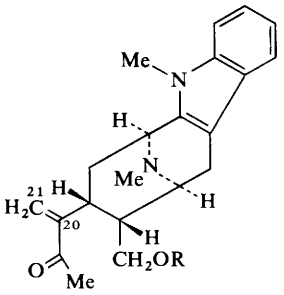


(214) R = H; Villamine
(216) R = Ac





(196), Pleiocarpamine

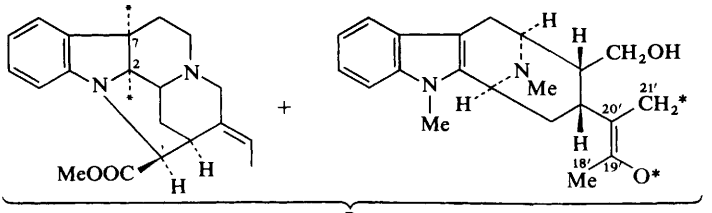


(215) R = H; Macroline
(217) R = Ac

species. The following mode of condensation (Scheme 12) is based on the greater nucleophilicity of the indole β-position compared to the α-position and leads to formulae (213) and (214) for villalstonine and villamine respectively. A model process for the primary step takes place during the acid-catalysed reaction of skatole with mesityl oxide to give the indoline (218).[121]

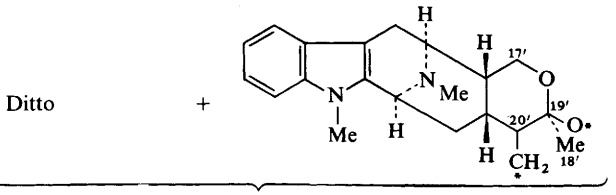
(*b*) Vigorous reduction of villalstonine with lithium aluminium hydride in tetrahydrofuran gives the diol (219). The cleavage of the ether function in the

[121] B. Robinson and G. F. Smith, *J. Chem. Soc.*, 1960, 4574.



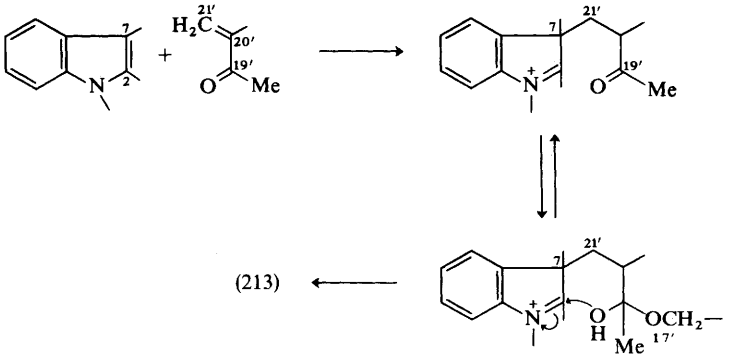
D

part structure for villamine



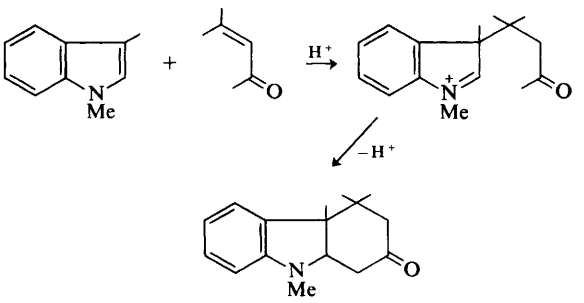
E

part structure for villalstonine

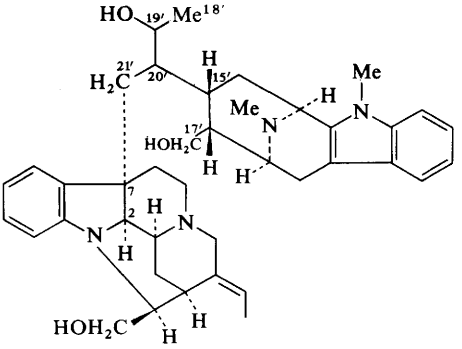


(213)

Scheme 12



(218)



(219)

manner shown suggests that it is present as a carbinolamine ether, *i.e.* C(2) rather than C(7) of the 2,7-dihydropleiocarpamine part is bound to the oxygen.[120]

The villalstonine formula readily allows an interpretation of the mass spectral fragment ions *m/e* 338 and 322 on the one hand, *m/e* 352 and 308 on the other. The genesis of these peaks begins with a decyclisation process in ring F (Scheme 13).

The constitution and relative stereochemistry of villalstonine has been subsequently confirmed independently by *X*-ray analysis of the base itself.[122] The formula shown (213) very probably represents the absolute configuration.

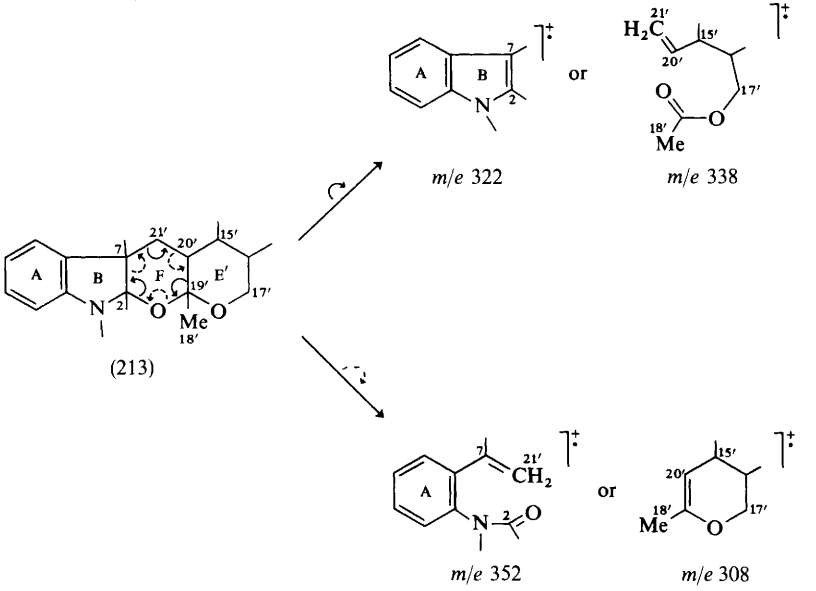
Finally, the more important arguments leading to the structure of macroline (215), $C_{21}H_{26}O_2N_2$, will be discussed: the presence of the groupings

CH_3–CO–$\overset{|}{C}$=CH_2 and >CH–CH_2OH follow from n.m.r. and i.r. spectra, that of the two *N*-methyl groups from n.m.r. The constitution follows from the mass spectral decomposition which involves two principal fragmentation modes which are shown in Scheme 14. This scheme is supported by, amongst other things, examination of the spectra of 20,21-dihydromacroline (catalytic hydrogenation product), the so-called macralinol (ketone function reduced with lithium aluminium hydride), and structurally related derivatives of ajmaline.[119]

Macralstonine (220).[71]—The dextrorotatory macralstonine, $C_{43}H_{52}O_5N_4$, is a bisindole alkaloid which is composed of two similar halves. As with villalstonine (213) the alkaloid undergoes fission in 2N-HCl. The results are summarised in Scheme 15.

The monomeric cleavage base alstophylline (221)[123] occurs naturally in *Alstonia macrophylla* Wall. Macroline (215) was previously isolated from villalstonine (213).[119] The cleavage ketone, $C_{20}H_{26}O_2N_2$, has been assigned structure (222) based on the following considerations: it is an indole and contains

[122] C. E. Nordman and S. K. Kumra, *J. Amer. Chem. Soc.*, 1965, **87**, 2059.
[123] T. Kishi, M. Hesse, C. W. Gemenden, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, 1965, **48**, 1349.



Scheme 13

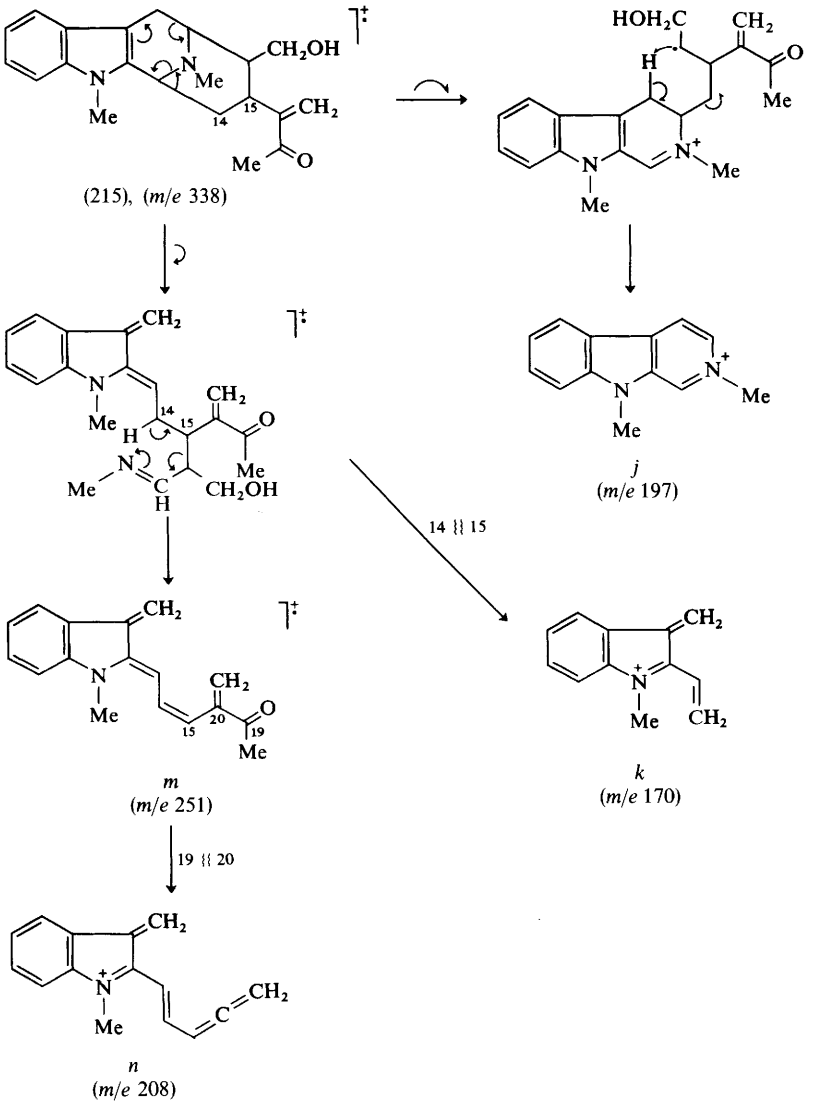
a primary hydroxy-group and a methyl ketone; in solution it exists as an equilibrium mixture of ketone and hemi-ketal; under the influence of acid the anhydro-product (223) is formed. The acid-catalysed cleavage of macralstonine (220) under deuteriating conditions gives a [$^2H_6$]alstophylline ($^2H_6$-221), a [$^2H_9$]ketone ($^2H_9$-222), and a [$^2H_8$]methoxy ketone ($^2H_8$-224).

The mass spectrum of the ketone (222) shows, as does that of macroline (215) (see Scheme 14), the peaks *m/e* 197 and 170. The macroline peaks at *m/e* 251 and 208 are now shifted 12 mass units lower to *m/e* 239 and 196, *i.e.* ketone (222) contains, instead of $>C{=}CH_2$, the grouping $>CH_2$. Structure (222) contains nine *C*-bonded exchangeable protons. The distribution shown in ($^2H_9$-222) has been confirmed mass spectrometrically.

Treatment of alstophylline with hot aqueous hydrochloric acid gives formic acid and the methoxy-ketone (224);[123] the latter exhibits the same mass spectrum as ketone (222) apart from the '30 m.u. methoxy-shift' of certain peaks.

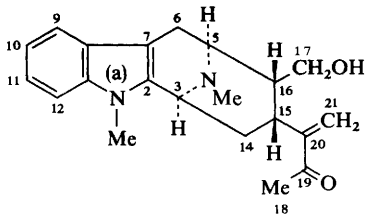
Since macroline (215) does not give ketone (222) under the above conditions, macralstonine (220) must break down by acid catalysis *via* two distinct processes: from one are formed alstophylline (221) and macroline (215), from the other alstophylline, ketone (222), and formaldehyde (Scheme 15). The two modes of cleavage can be understood in terms of structure (220) as shown in Scheme 16.

When heated at 300–350 °C under high vacuum, macralstonine (220) loses water to give anhydromacralstonine (225), which can also be obtained by treat-

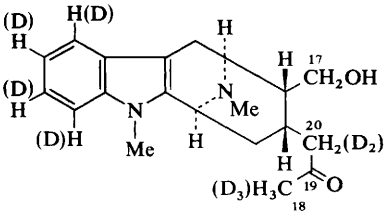


Scheme 14

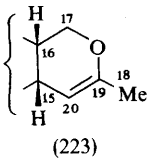
ment of the parent alkaloid with hydrochloric acid in alcohol-free chloroform. The u.v. spectrum of (225) is a summation of those of alstophylline (221) and the ketone (222). In the i.r. spectrum the bands of the grouping $-O-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$ can be recognised (1650 and 1621 cm^{-1}).



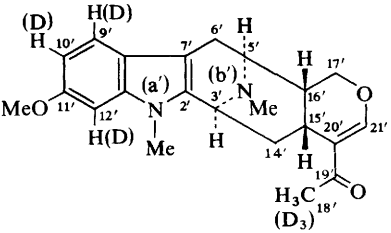
(215), Macroline



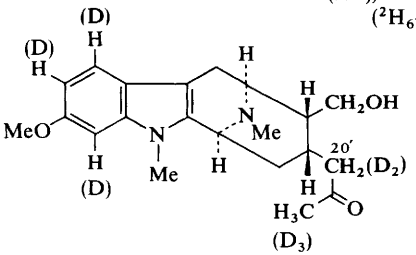
Ketone (222)
($^2H_9$-222)



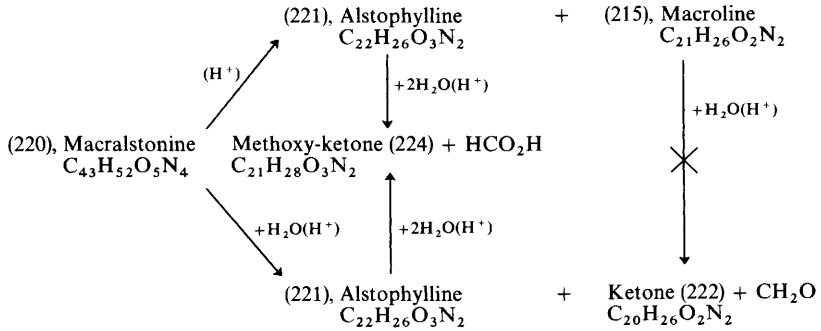
(223)



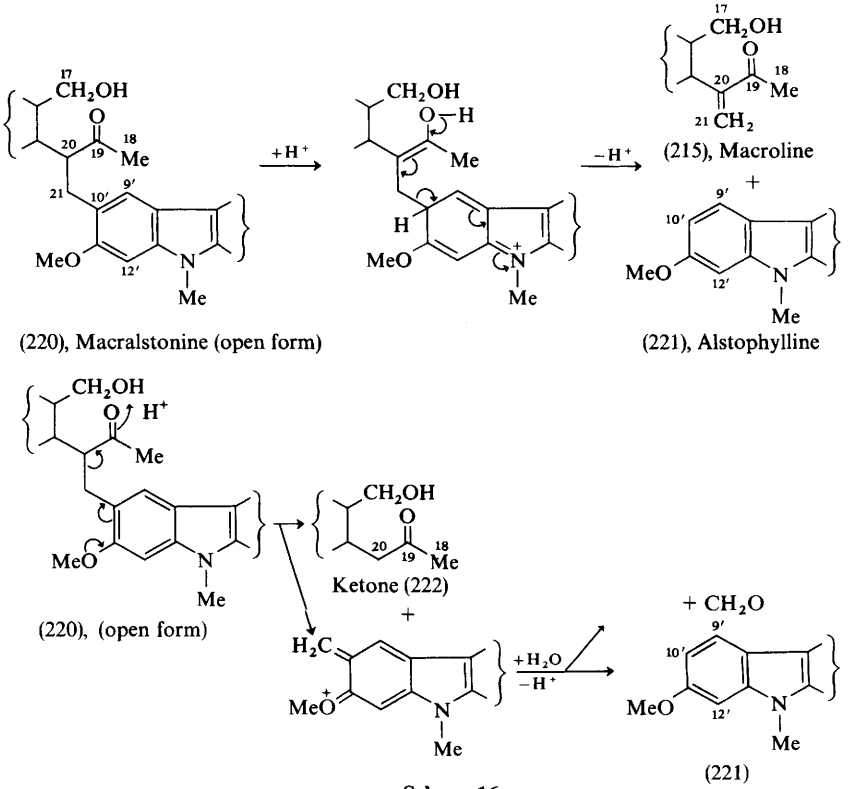
(221), Alstophylline
($^2H_6$-221)



Methoxy-ketone (224)
($^2H_8$-224)



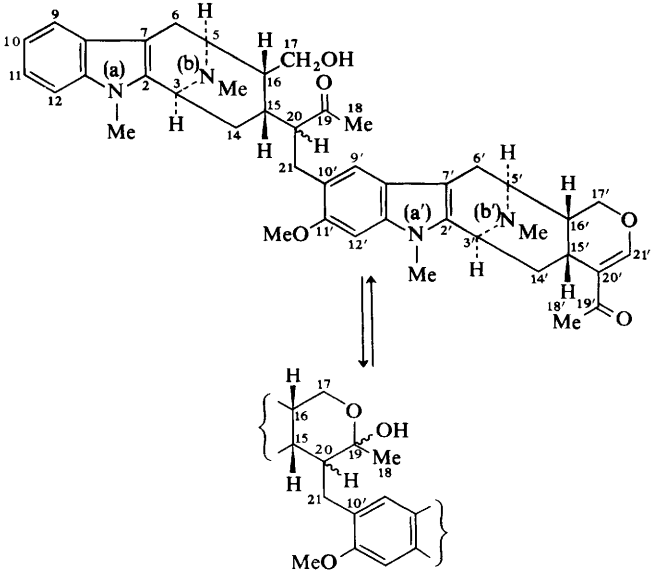
Scheme 15



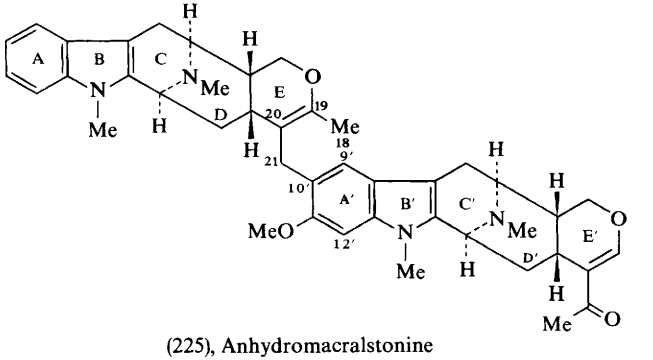
Scheme 16

The possible positions of coupling between the two 'halves' are those carbon atoms which are deuteriated in [$^2H_6$]alstophylline ($^2H_6$-221) and the [$^2H_9$]ketone ($^2H_9$-222) formed on cleavage under deuteriating conditions. The n.m.r. spectrum of anhydro-macralstonine (225) shows a doublet at 7.30 p.p.m. [C(9)-H] and two singlets at 6.69 and 6.31 p.p.m [C(9')-H and C(12')-H]; three further aromatic protons give rise to a multiplet at 6.9 p.p.m. The total aromatic proton count is therefore six, two of which can have no *ortho* neighbours and whose signals show no *meta*-coupling in the n.m.r. spectrum. This points to C(10') as the point of coupling to the macroline component. On biogenetic grounds also this would seem much more likely than C(9'). The C(21')-proton appears as a singlet at 7.40 p.p.m. [7.52 p.p.m. in alstophylline (221)]. Also of importance are the two *C*-methyl singlets in the 2 p.p.m. region. Since anhydromacralstonine (225) contains six aromatic protons and 2 $-\overset{|}{\underset{|}{C}}-CH_3$ groups, and the d_9-ketone (d_9-222) only contains deuterium, in the aliphatic part, at C(18) and C(20), C(21) of the macroline part must be coupled to C(10') of the alstophylline part as shown in (225).

The mass spectrum of anhydromacralstonine (225) exhibits typical macroline (215) peaks in the lower mass region (see Scheme 14); in contrast, the corresponding alstophylline (221) peaks are absent. Of those peaks in the high mass region giving important indications of the 'dimeric' structure, only that at *m/e* 379 (*o*)



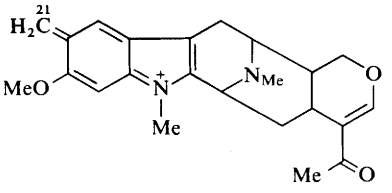
(220), Macralstonine



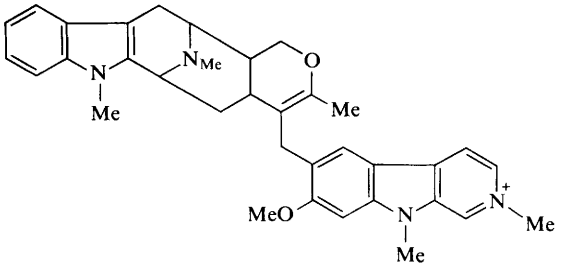
(225), Anhydromacralstonine

will be discussed.* This peak confirms the coupling of C(21) of the macroline part to the benzene nucleus of the alstophylline part. The other ions are formed by fragmentations in rings C,D, and E as well as C′,D′, and E′, which also occur in the cases of the monomers.

* The ion *m/e* 547 ($C_{35}H_{39}O_2N_4$) which is not discussed in ref. 71 is assigned structure *p*.



o
(*m/e* 379)



p
(*m/e* 547)

Macralstonine is the water-addition product of (225). This addition cannot be at the β-keto-enol ether system of the alstophylline 'half' since macralstonine shows the same u.v. absorption as the anhydro-compound (225), bands at 1646 and 1615 cm^{-1} in the i.r. spectrum, and the low-field singlet of the C(21')-proton in its n.m.r. spectrum. Hydration must therefore be at the double bond of the macroline component, resulting in structure (220) for macralstonine. In chloroform both the ring-open and ring-closed forms are present [singlets for the $-C(18)H_3$ grouping at 1.67 and 1.49 p.p.m. (total 3H) and a medium ketone band at 1706 cm^{-1}]. The presence of two distinct species causes other n.m.r. signals to be doubled, a fact which does not facilitate interpretation.

The biosynthesis of macralstonine is considered to involve a Michael-type coupling of the nucleophilic centre of alstophylline to macroline.

Macralstonidine (226).[124]—The dextrorotatory macralstonidine (226), $C_{41}H_{48}O_3N_4$, like its relatives, is cleaved readily in concentrated hydrochloric acid to ketone (222), $N_{(a)}$-methylsarpagine (227),* and formaldehyde according to the equation:

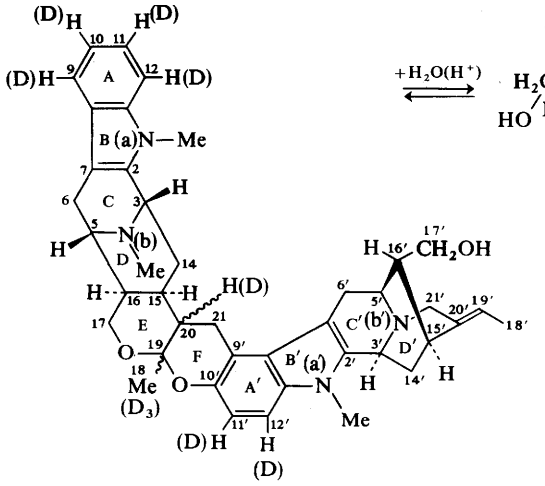
$$\underset{(226)}{C_{41}H_{48}O_3N_4} + 2H_2O \xrightarrow{(H^+)} \underset{(222)}{C_{20}H_{26}O_2N_2} + \underset{(227)}{C_{20}H_{24}O_2N_2} + CH_2O$$

[124] E. E. Waldner, M. Hesse, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 1926.

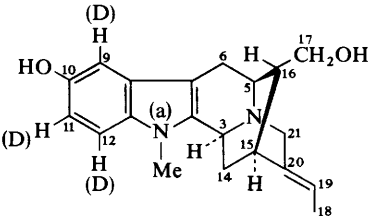
* The absolute configuration shown is not proven.[124]

Simultaneous production of ketone (222) and formaldehyde strongly suggests that a building block of macralstonidine, as with villalstonine (213) and macralstonine (220), is the base macroline (215). In addition, it is probable that the mechanism of the cleavage process corresponds to that of macralstonine which leads to the formation of alstophylline (221), ketone (222), and formaldehyde (see Scheme 16).

In the light of the following observations the structure (226) may be postulated for macralstonidine:



(226), Macralstonidine
($^2H_{10}$-226)



(227), $N_{(a)}$-Methylsarpagine
($^2H_3$-227)

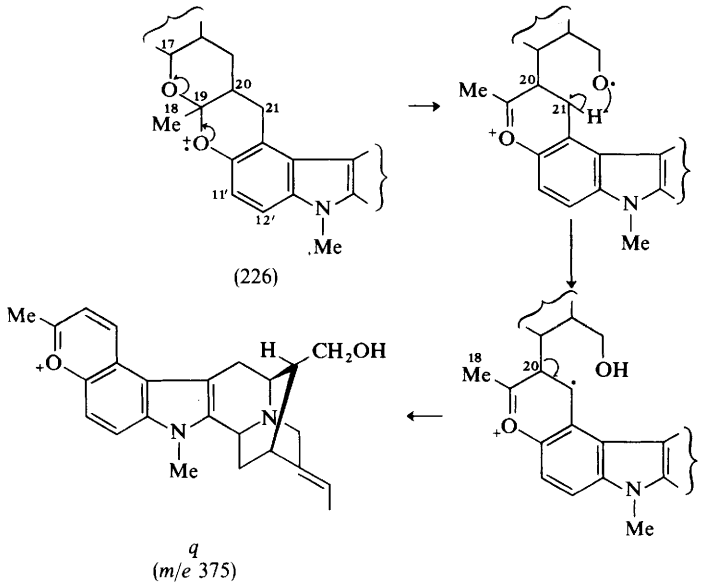
(*a*) The u.v. spectrum, identical to an addition of *N*-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole and ketone (222) absorptions, is not shifted on addition of alkali. The phenolic hydroxy-group of the sarpagine component is therefore involved in the coupling between the two 'halves'.

(*b*) Macralstonidine contains a primary hydroxy-group (mono-*O*-acetyl derivative and aldehyde formation).

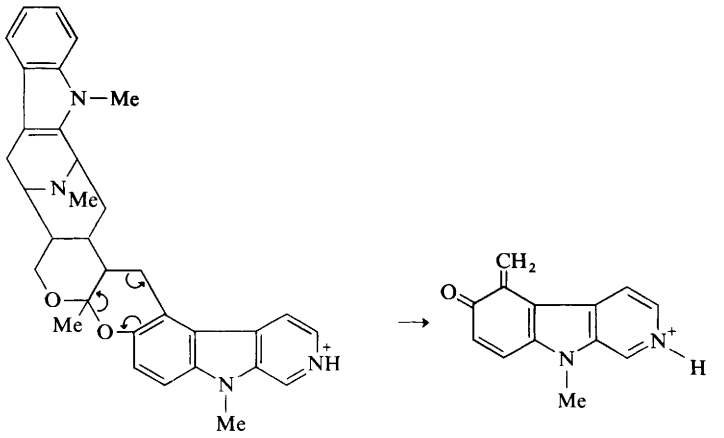
(*c*) The keto-groups of macroline (215) and ketone (222) are absent in the dimer. (*d*) The n.m.r. spectrum shows signals for six aromatic protons, two of which form an *AB*-system. Also observed are the signals of an ethylidene group, the three *N*-methyl groups, and a tertiary C–CH_3 group (singlet at 1.36 p.p.m.).

The macralstonidine structure (226) has been confirmed by D-exchange experiments and mass spectroscopy. Partial solvolysis of the alkaloid in DCl–D_2O, after exchange of *O*-bound deuterium, gives the nonadeuteriated ketone ($^2H_9$-222) [also obtained from macralstonine (220)], [9,11,12-$^2H_3$]-$N_{(a)}$-methylsarpagine ($^2H_3$-227), and [9,10,11,12,18,18,18,20,11′,12′-$^2H_{10}$]macralstonidine($^2H_{10}$-226). The incorporation of deuterium at C(18) and C(20) is due to the formation of the hydroxy-ketone form (228) of macralstonidine. It is this species which must undergo cleavage to formaldehyde, ketone (222), and $N_{(a)}$-methylsarpagine (227). The deuteriation experiments are thus in complete accord with structure (226) for macralstonidine.

The mass spectrum of the alkaloid shows the typical macroline (215) peaks at *m/e* 251, 197, and 170 (see Scheme 14). Heavier fragments arise by fragmentation of (*a*) the macroline part, (*b*) the sarpagine part, and (*c*) the six-membered ring F which holds the two 'halves' together. Examples of each type are given below. (*a*) The molecular ion with the positive charge on the phenolic oxygen undergoes cleavage of a ketal bond (Scheme 17); a hydrogen is transferred from C(21) to the oxygen radical followed by radical cleavage to the pyrylium cation *q*, *m/e* 375, which is shifted to *m/e* 381 in the mass spectrum of [$^2H_{10}$]macralstonidine ($^2H_{10}$-226).

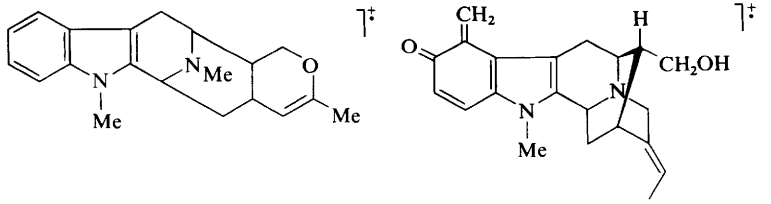


Scheme 17



r (*m/e* 519) *s* (*m/e* 211)

Scheme 18



t (*m/e* 308) *u* (*m/e* 336)

(*b*) Fragmentation of a macralstonidine molecular ion in a manner characteristic of sarpagine[125] gives the fragment ion *r*, *m/e* 519, which as shown dissociates to the ion *s*, *m/e* 211 (Scheme 18). In the spectrum of [$^2H_{10}$]macralstonidine ($^2H_{10}$-226) *r* is shifted by ten mass units, *s* by two mass units.

(*c*) A retro-Diels–Alder reaction in ring F of the macralstonidine (226) molecular ion gives, depending on the charge location, the ions *t*, *m/e* 308, or *u*, *m/e* 336.* The corresponding ions from ($^2H_{10}$-226) are shifted by eight and two mass units respectively.

If it is assumed that macralstonidine (226) is formed in the plant from the bases macroline (215) and $N_{(a)}$-methylsarpagine (227), the immediate Michael-addition product would be the hydroxy-ketone species (228).

[125] Ref. 5, p. 81.

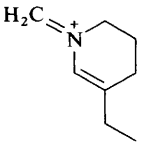
* This ion can also be formed *via* processes involving hydrogen (or deuterium) shifts.

13 Pleiomutine and Umbellamine

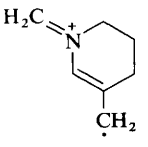
These two bases, pleiomutine from *Pleiocarpa mutica* Benth. and umbellamine from *Hunteria umbellata* (K. Schum.) Hall. F. (*Carpodinus umbellatus* K. Schum., *Polyodoa umbellata* Stapf., *Picralima umbellata* Stapf.), possess a common building block, namely 14,15-dihydroeburnamenine (229). This is bonded through C(14) to the aromatic ring of the second monomeric component, an indoline. Umbellamine is probably identical with the alkaloid hunterine, of unknown constitution, from *Hunteria eburnea* Pichon.[126]

(−)-Pleiomutine (230).[115,127,128]—The alkaloid, molecular formula $C_{41}H_{50}O_2N_4$, contains the functional groups $>N_{(a)}-CH_3$, $-COOCH_3$, and $-\underset{}{\overset{\diagdown}{\overset{}{C}}}-CH_2-CH_3$. This last group gives rise to a methyl triplet in the n.m.r. spectrum, which in position and character is typical of the methyl triplet associated with alkaloids of the eburnamine type; the idea that pleiomutine (230) is a derivative of eburnamine (231) thus emerged.

The mass spectral peaks *m/e* 124 (*v*) and 109 (*w*),[129] together with the $N_{(a)}$-methyl and methoxycarbonyl groups, indicate that the second component is pleiocarpinine (232). Significantly, pleiocarpinine and eburnamine (231) both occur in *Pleiocarpa mutica* Benth. In fact, when pleiomutine (230) is warmed in 4N-HCl at 90 °C, pleiocarpinine (232) can be isolated together with unchanged starting material. The eburnamine part is destroyed. On refluxing in acid the so-called pleiomutinone (233) is formed with elimination of methanol. This behaviour, resulting in the formation of a five-ring ketone, parallels that originally noted with monomeric alkaloids of the pleiocarpinine (232) type.[130]



v
(*m/e* 124)



w
(*m/e* 109)

Reductive cleavage of pleiomutine with zinc and hydrochloric acid gives mainly one product, whose mass spectrum is identical to that of 14,15-dihydroeburnamenine (229). These results allow the hydrolysis of pleiomutine to be

[126] Y. Morita, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1969, **52**, 89, 1784.
[127] M. Hesse, F. Bodmer, and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 964.
[128] D. W. Thomas, H. Achenbach, and K. Biemann, *J. Amer. Chem. Soc.*, 1966, **88**, 1537.
[129] C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. Kump, D. J. Le Count, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, 1963, **46**, 742.
[130] C. Kump, J. J. Dugan, and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 1237.

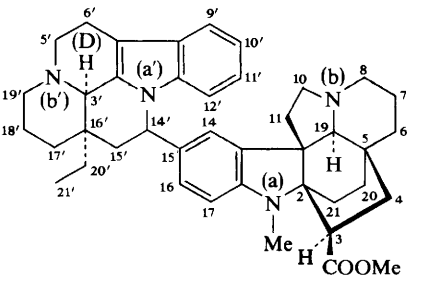
formulated as follows:

$$\underset{(230)}{C_{41}H_{50}O_2N_4} + H_2O \xrightarrow{H^+} \underset{(232)}{C_{22}H_{28}O_2N_2} + \underset{(231)}{C_{19}H_{24}ON_2}$$

The eburnamine (231) is subsequently destroyed by the acid; in the presence of zinc it is stabilised by reduction to 14,15-dihydroeburnamenine (229).

The structure (230) for pleiomutine is practically proved by a biosynthetic-like partial synthesis from (−)-pleiocarpinine (232) and (−)-eburnamine (231). Condensation proceeds in cold 1N acid or by heating in 2 % hydrochloric acid. Synthetic and natural material show the same rotation, and formula (230) thus represents the absolute configuration.* Eburnamenine (234) under the same conditions does not react with pleiocarpinine (232). The only reaction which could logically lead to a union of (231) and (232) is substitution of the potentially electrophilic C(14) of eburnamine (231) at one of the nucleophilic centres, C(15) or C(17), of pleiocarpinine (232). The 14′,15-coupling proposed in (230) takes the greater nucleophilicity of C(15) and the steric hindrance around C(17) into account.

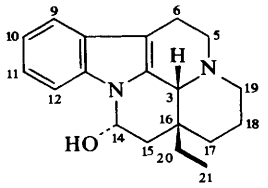
The n.m.r. spectrum (CCl_4) of pleiomutine confirms structure (230): the aromatic region contains signals due to seven protons. At 6.27 p.p.m. occur two overlapping doublets with *ortho* coupling, which must correspond to the C(17)- and C(12′)-protons. Hence, C(15) must be a point of linkage. The C(12′)-hydrogen resonates at *ca.* 0.7 p.p.m. higher field than in the corresponding monomer for which the equatorial arrangement of the pleiocarpinine residue at C(14′) is responsible. The axial C(14′)-proton gives rise to a quartet (J_1 = 12 Hz, J_2 = 5.5 Hz; X part of an ABX-system) at 4.85 p.p.m.; J_1 corresponds to an axial–axial coupling. The two n.m.r. arguments thus lead to the same conclusion. The relative configuration at C(14′) is, however, unknown.



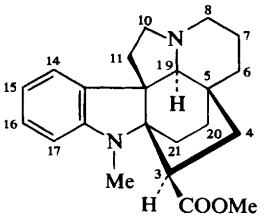
(230), Pleiomutine

[131] A. Guggisberg, A. A. Gorman, B. W. Bycroft, and H. Schmid, *Helv. Chim. Acta*, 1969, **52**, 76.

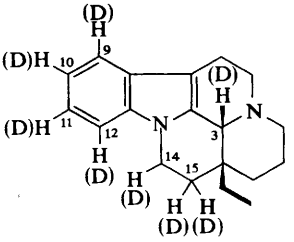
* Concerning the absolute configuration of (−)-pleiocarpinine (232) see ref. 131.



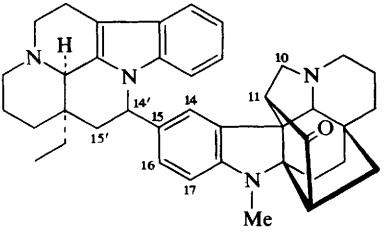
(231), (−)-Eburnamine



(232), (−)-Pleiocarpinine



(229), 14,15-Dihydroeburnamenine
(234), $\Delta^{14,15}$; Eburnamenine



(233) Pleiomutinone

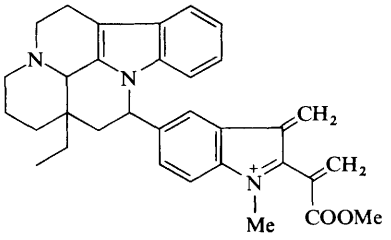
D-exchange experiments also confirm the proposed structure.[128] Reductive cleavage of pleiomutine under deuteriating conditions (Sn with *ca.* 4N-D_3PO_4–DCl; reflux) gives a mixture of [9,10,11,12,14,15,15-$^2H_7$]-14,15-dihydroeburnamenine ($^2H_7$-229) and [3,9,10,11,12,14,15,15-$^2H_8$]-14,15-dihydroeburnamenine ($^2H_8$-229). The deuteriums bound to the aromatic nucleus and C(3) can be exchanged by warming in 4N-HCl to give [14,15,15-$^2H_3$]-14,15-dihydroeburnamenine ($^2H_3$-229), the location of the deuterium being determined mass spectrometrically. The presence of deuterium at C(14) shows that this centre must be linked to the pleiocarpinine unit in the 'dimer'.

Deuteriation of pleiomutine (230) under mild conditions yields [17,9′,10′,11′,12′-$^2H_5$]pleiomutine ($^2H_5$-230), whose n.m.r. spectrum ($CDCl_3$) shows a singlet at 7.16 p.p.m. corresponding to the two *meta* aromatic protons of the indoline component. Under mild conditions it is possible to wash out selectively the indoline deuteron at C(17). The aromatic region of the n.m.r. spectrum now shows only the character of an *ABM*-system composed of a doubled doublet with *ortho* and *meta* coupling [C(16)-H] and two simple doublets with *meta* [C(14)-H, 7.14 p.p.m.] and *ortho* [C(17)-H, 6.53 p.p.m.] coupling. If the 14,15-dihydroeburnamenine component were linked to C(17) one would anticipate an A_2M-system with two doublets and a triplet.

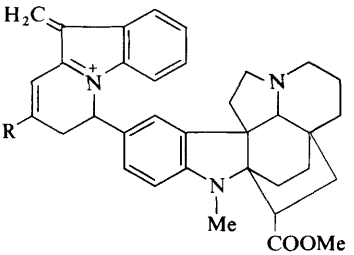
The constitution of pleiomutine (230), apart from the decision in favour of C(15) or C(17) as a linkage position, can be established from the mass spectrum of the alkaloid. In the low-mass region fragments *m/e* 278, 249, and 208, characteristic of eburnamenine,[132] are apparent, as well as the previously mentioned fragments *v* and *w* and the $M^+ - 28$ peak,[129] all typical of pleiocarpinine (232).

[132] H. K. Schnoes, A. L. Burlingame, and K. Biemann, *Tetrahedron Letters*, 1962, 993.

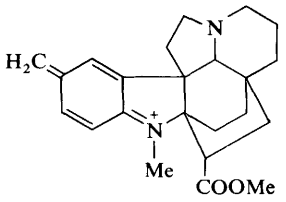
Other ions arise due to loss of fragments from the molecular ion of the 'dimeric' alkaloid. If the pleiocarpinine component is involved then, amongst others, the ion *x* (*m/e* 506) is formed; if the eburnamine part is involved peaks due to the ions *y* (*m/e* 560) and *z* (*m/e* 601) are observed. In addition, peaks at *m/e* 365 (*aa*) and



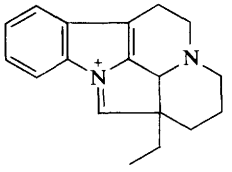
x
(*m/e* 506)



y: R = C_2H_5; *m/e* 560
z: R = $(CH_2)_3$—N=CH_2; *m/e* 601



aa
(*m/e* 365)



ab
(*m/e* 265)

265 (*ab*) are produced which clearly demonstrate the nature of the linkage between the two 'halves'. The structures for these fragment ions are supported by the mass spectral behaviour of pleiomutinone (233).

(−)-Umbellamine (235)[126].—The alkaloid umbellamine (235), $C_{41}H_{48}O_4N_4$, isolated from *Hunteria umbellata*, was immediately striking owing to its mass spectral behaviour. An incompletely pure sample shows two peaks in the mass spectrometer (vaporisation temperature 380 °C) at *m/e* 660 and 674. With progressively longer measuring time the latter peak increases at the expense of the former. Further, in the middle-mass region, peaks characteristic of eburnamenine (234) begin to appear until finally only the mass spectrum of eburnamenine remains. With completely pure material this thermal behaviour is much less pronounced.

The above observations led to a preparative pyrolysis* of umbellamine (235). Heating at 330 °C for 30 min in a Pyrex tube gives, along with higher molecular weight material, a 40% yield of pure (+)-eburnamenine (234).†

* The formation of eburnamenine (234) presumably involves either a radical cleavage reaction or a cyclic process affording (234), water, and a dehydrobenzene derivative of the second monomeric unit. Pleiomutine (230) does not undergo this reaction.

† A dehydroeburnamenine, probably the 5,6-dehydro-compound, is also formed in small amounts.

The i.r. spectrum of umbellamine (235) shows an ester or six-ring lactone band. In the n.m.r. it shows signals due to six aromatic protons and two methyl singlets at 2.83 and 2.78 p.p.m., which according to a Zeisel determination correspond to one *O*-methyl and one *N*-methyl group. In addition, the methyl triplet of the eburnamenine (234) ethyl group is apparent at 0.86 p.p.m. Kuhn–Roth oxidation in conjunction with a partly obscured doublet in the n.m.r. shows the presence of a second *C*-methyl group, which is present as part of an ethylidene grouping (double resonance).

Umbellamine possesses a phenolic hydroxy-group (bathochromic shift of the long wavelength u.v. maximum from 295 to 309 nm in alkali; formation of an *O*-acetyl derivative and a methyl ether (236) with diazomethane in dimethyl formamide–ether), which must be in the unknown component. This 'half' of umbellamine (235) appears from i.r. and n.m.r. evidence, and the formation of only an *O*-acetyl derivative, to be an *N*-methylindoline.

The u.v. spectrum of umbellamine cannot, however, be satisfactorily synthesised from the addition of the spectra of eburnamine (231) and any one of the four phenolic hydroxy-*N*-methylindolines.

O-Methylumbellamine (236), on lithium aluminium hydride reduction, is converted to diol (237), $C_{41}H_{52}O_3N_4$ [same u.v. as (236), no C=O absorption in the i.r. spectrum], which forms an *OO*-diacetyl derivative. Reduction with $LiAlD_4$ gives [2′,22′,22′-$^2H_3$]-diol (237)($^2H_3$-237).

Mild lithium aluminium hydride reduction of *O*-methylumbellamine (236) gives the alcohol (238), $C_{41}H_{50}O_3N_4$ (no C=O band), which forms a mono-*O*-acetyl derivative. The reduction experiments demonstrate the presence of a methoxycarbonyl function and indicate that the fourth oxygen is very probably present in a carbinolamine ether grouping.

The mass spectrum of diol (237) shows peaks at *m/e* 252, 237, and 197 characteristic of the dihydroeburnamenyl residue which also appear in the spectrum of pleiomutine (230) (see preceding Section). Peaks appearing at *m/e* 196, 178, and 166 are characteristic for the aliphatic part of pseudoakuammigol (239).[133]

Table 2

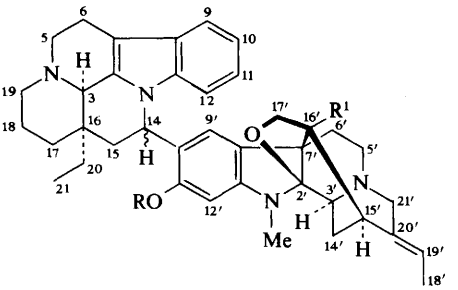
Compound	M^+	$M-OH$	$M-CH_2OH$	*Other peaks*	*ac*	$ac-H_2O$	$ac-CH_2O$
diol (237)	648	631	617	573 466 452	196	178	166
	340[a]	323[a]	309[a]	265[a] 158[a] 144[a]			
pseudoakuammigol (239)	340	323	309	265 158 144	196	178	166

[a] Mass of eburnamenine (278) + CH_2O (30) (= 308) subtracted.

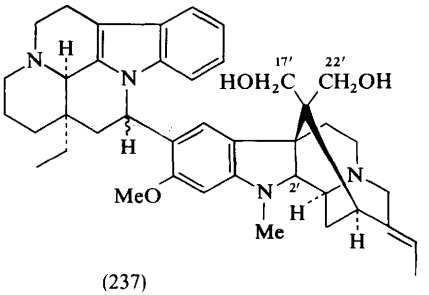
In Table 2 a comparison of the mass spectra of diol (237) and pseudoakuammigol[133] is shown. If the mass of eburnamenine (*m/e* 278) plus CH_2O (30, to correct for the methoxy-group) is subtracted from the peaks in the high-mass

[133] Ref. 5, p. 146.

region of the spectrum of (237), all pseudoakuammigol peaks corresponding to fragments containing the aromatic nucleus are obtained. Diol (237) and umbella-



(235) R = H, R^1 = CO_2Me; Umbellamine
(236) R = Me, R^1 = CO_2Me
(238) R = Me, R^1 = CH_2OH



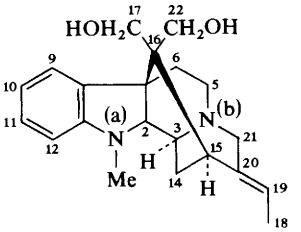
(237)
($^2H_3$-237) [2′,22′,22′-$^2H_3$]

mine (235) are thus composed of a dihydroeburnamenyl residue which is linked to a methoxy-pseudoakuammigol and a hydroxy-pseudoakuammigine respectively.

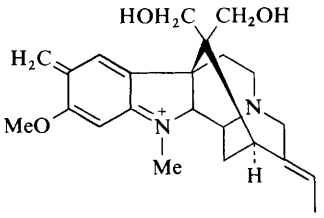
The peak *m/e* 265 (*ab*) (see preceding Section) in the mass spectrum of diol (237) shows that the linkage position in the dihydroeburnamenyl part is C(14). The fragment *m/e* 383 (*ad*), which corresponds to *aa* of the pleiomutine (230) spectrum, and the peaks in the region *m/e* 648 to *m/e* 452 (Table 2), show that an aromatic carbon of the pseudoakuammigol part is involved in the 'dimeric' linkage.

That the carbinolamine ether function is at C(2′) rather than C(5′) or C(21′) is shown by the shift of the fragment ion *ac* (*m/e* 196) in the spectrum of diol (237) to *m/e* 198 in that of ($^2H_3$-237) (*ae*).

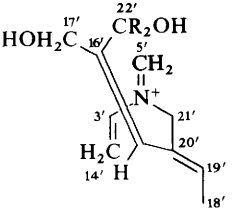
An analysis of the aromatic region of the n.m.r. spectrum of umbellamine (235), *O*-acetylumbellamine, and *O*-methylumbellamine (236) shows that the benzene ring of the pseudoakuammigine 'half' contains protons at C(9′) and C(12′): the region from 7.5 to 6.65 p.p.m. in the spectrum of umbellamine contains, as verified



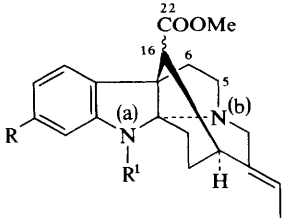
(239), Pseudoakuammigol



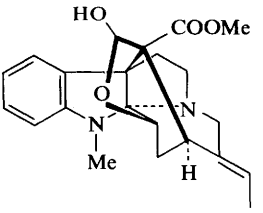
ad
(*m/e* 383)



ac: R = H; *m/e* 196
ae: R = D; *m/e* 198



(240) R = OH, R^1 = Me
(241) R = R^1 = H; Isodihydrostrictamine



(242), Corymine

by double-resonance experiments, the signals due to the protons at C(9), C(10), and C(11) of the dihydroeburnamenyl part. The centre of a multiplet resulting from overlap of the doublet of the C(12)-H (decoupling) and the singlet of the C(9′)-H of the pseudoakuammigine part lies at 6.52 p.p.m. and the *singlet* C(12′)-H signal appears at 6.10 p.p.m.* A decision between the two alternative structures, (235) and 10′-hydroxy-11′-[14-(14,15-dihydroeburnamenyl)]pseudoakuammigine is not possible from n.m.r. data.

The acid-catalysed cleavage of the alkaloid gives, with the exception of formaldehyde, no clearly defined product. However, under reductive cleavage

* In the experimental part of ref. 126 the C(9)-H and C(12)-H were erroneously interchanged.

conditions (HCl with Zn or Sn) an isodihydrostrictamine derivative (240, $M = 354$) is formed in poor yield. This base, which has not been obtained in a completely pure state, does not show the strictamine peak at *m/e* 194.[134] Its u.v. spectrum, λ_{max} 260 and 296 nm, is that of a hydroxy-indoline; in acid it undergoes a hypsochromic shift of 8—9 nm, in alkali a bathochromic shift of 11 nm. The acid shift is typical of α-amino-indoline systems.

The formation of (240) proceeds by way of a C(2′)-$N_{(a')}$ indoleninium salt and is similar to the conversion of strictamine to isodihydrostrictamine (241).* Since the base (241) shows a practically normal indoline u.v. spectrum it would appear reasonable to compare the u.v. spectrum of the umbellamine cleavage product (240) with those of hydroxy- or methoxy-indolines. 2,3-Disubstituted indolines with a 6-hydroxy- or 6-methoxy-group show an extinction coefficient ratio, short wavelength band to long wavelength band, of 1.2—1.5 while in the case of the 5-hydroxy- and 5-methoxy-derivatives the ratio is 2—3 (see ref. 70). For the degradation product (240) a ratio of 1.3 is found, which indicates strongly that umbellamine possesses a hydroxy-group in the 11′-position and has the structure (235). The substitution in the indoline part thus corresponds to that in the 'dimers' of the vinblastine type (Section 10).

The strong shielding of the $-COOCH_3$ group by approximately 1 p.p.m., which is not solvent-dependent, is due to the anisotropic effect of the aromatic system of the dihydroeburnamenine component.

In structure (235) the stereochemistry of the pseudoakuammigine part is relative, although it probably corresponds to the absolute configuration, since the alkaloid corymine (242) of known absolute configuration occurs in the leaves and seeds of *Hunteria umbellata.* It has not yet been encountered in the root bark of the plant which contains umbellamine and other bisindole alkaloids.

Lack of the necessary monomers has prevented attempts at the partial synthesis of umbellamine. The remarks concerning the biogenesis of pleiomutine (230) apply also to umbellamine.

14 Gabonine[135]

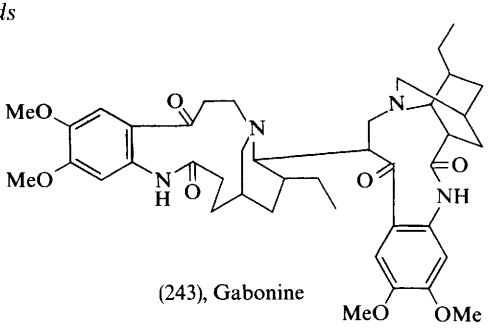
This dextrorotatory alkaloid ($C_{42}H_{56}O_8N_4$; analysis; mass spectrum) was isolated many years ago from *Tabernanthe iboga* Baillon. It exhibits u.v. absorption which is identical to that of 2-acetamido-4,5-dimethoxybenzaldehyde. The i.r. spectra of the alkaloid and this model compound are also very similar in the 1600—1700 cm^{-1} region. In the n.m.r. four singlets are observed which correspond to two $>NH$ protons, two kinds of aromatic proton (two of each), and four aromatic methoxy-groups. Signals for $-CH_2CH_3$ groups are also apparent.

On the basis of these data the structure (243) has been proposed as a working hypothesis for gabonine. This requires that in this unsymmetrical structure the

[134] H. K. Schnoes, K. Biemann, J. Mokry, I. Kompiš, A. Chatterjee, and G. Ganguli, *J. Org. Chem.*, 1966, **31**, 1641.

[135] W. I. Taylor, *J. Org. Chem.*, 1965, **30**, 309.

* This also shows a hypsochromic acid shift of 8–9 nm.



(243), Gabonine

two >NH protons, the four methoxy-groups, and each set of aromatic protons are magnetically equivalent.

15 Serpentinine[136]

The deep-yellow base serpentinine, first isolated from *Rauwolfia serpentina* Benth. ex Kurz and later from other related species, possesses the molecular formula $C_{42}H_{44}O_6N_4$, based on elemental analyses and molecular weight determinations. The anhydrous compound is hygroscopic and crystallises with 1—2 moles of water.[137,138] The analyses of a number of salts agree with this formula.

The u.v. spectrum of serpentinine corresponds to an addition of the absorption of serpentine (244) or alstonine (245) to that of yohimbine (246). In accordance with this, serpentinine in aqueous dimethylformamide exhibits two pK'_a values of 6.0 (tetrahydro-β-carboline part) and 10.6 (anhydronium base part); pK'_a of serpentine (244) = 10.8.[137] The presence of a grouping $R{-}O{-}\overset{|}{C}{=}\overset{|}{C}{-}COOCH_3$ is supported by i.r. bands (Nujol, KBr) at 1701—9 and 1616 cm^{-1}. A 'normal' ester group is also present (1730 cm^{-1}). As already mentioned, the u.v. spectrum of serpentinine corresponds to an addition of the spectra of alstonine (245) and yohimbine (indole chromophore), rather than of alstonine (245) and tetrahydroalstonine (247). Serpentinine therefore possesses only one β-alkoxy-acrylic ester function. This agrees with the formation of a methanol addition product, monomethoxydihydroserpentinine, whose u.v. spectrum corresponds to an addition of tetrahydro-β-carboline and anhydronium base chromophores.[139]

In the n.m.r. spectrum ($CDCl_3$) of serpentinine the two $-COOCH_3$ singlets at 3.75 and 3.45 p.p.m. are observed, as are the doublets at 1.90 and 1.23 p.p.m. of the two *C*-methyl groups (Kuhn–Roth), which must therefore be secondary.

[136] H.-G. Boit; Ergebnisse der Alkaloid-Chemie bis 1960. Akademie-Verlag, Berlin 1961, p. 554; J. E. Saxton, 'The Indole Alkaloids,' in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VII, 1960, p. 96; R. H. F. Manske, 'Alkaloids of Pseudocinchona and Yohimbe,' in 'The Alkaloids,' ed. R. H. F. Manske, Vol. VIII, 1965, p. 713.

[137] C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *J. Amer. Chem. Soc.*, 1957, **79**, 1217.

[138] H. Kaneko, *J. Pharm. Soc. Japan*, 1960, **80**, 1357, 1362, 1365, 1370, 1374, 1378, 1382; *Chem. Abs.*, 1961, **55**, 6511*e*—6514*a*.

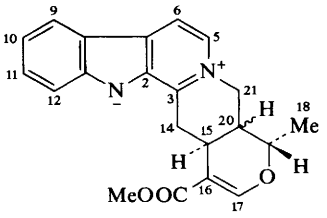
[139] M. Hanaoka, G. Englert, A. A. Gorman, M. Hesse, and H. Schmid, unpublished results.

A strong band at 3330 cm^{-1} in the i.r. spectrum ($CHCl_3$) of serpentinine is due to an indolic NH group; serpentine (244) shows no such band.

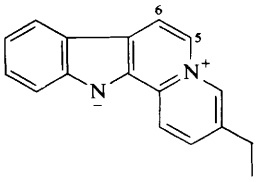
Potassium fusion of serpentinine gives indole-2-carboxylic acid and 1-oxo-1,2-dihydro-β-carboline.[140] Dehydrogenation with selenium gives alstyrine (112); with Pd–C the following compounds have been isolated in low yield: desethylalstyrine, flavopereirine (248), 5,6-dihydroflavopereirine (249), and two compounds *B* and *F*. If it is assumed that the flavopereirine (248) comes from the anhydronium base part and the 5,6-dihydroflavopereirine from the tetrahydro-β-carboline part, then formation of (248) and (249) together with the presence of two $>CH-CH_3$ groupings and the β-alkoxy-acrylic ester and normal ester groupings shows that serpentinine is comprised of two heteroyohimbine units.[138]

On the basis of u.v. and i.r. spectra the degradation products *B* and *F* are dimeric in nature and are assigned the part structures shown.

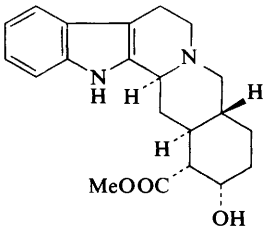
From these observations and the fact that serpentine (244) and ajmalicine [stereoisomer of tetrahydroalstonine (247)] also occur in *Rauwolfia serpentina* the formula (250) has been proposed for serpentinine.[138]



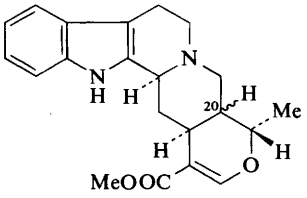
(244) 20β-H; Serpentine
(245) 20α-H; Alstonine



(248), Flavopereirine
(249) 5,6-Dihydro



(246), Yohimbine

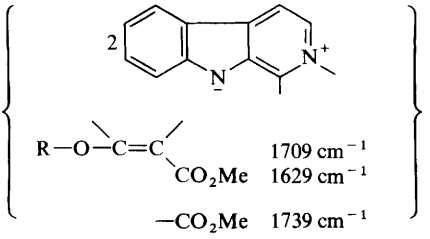


(247) 20α-H; Tetrahydroalstonine
(254) 20β-H; Ajmalicine

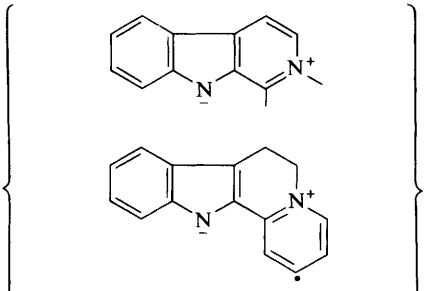
Unfortunately the mass spectrum of serpentinine shows only peaks corresponding to thermal decomposition products.

Reduction of the 'dimer' in methanol with sodium borohydride gives two diastereoisomeric tetrahydroserpentinines (251) and (252), whose u.v. spectra

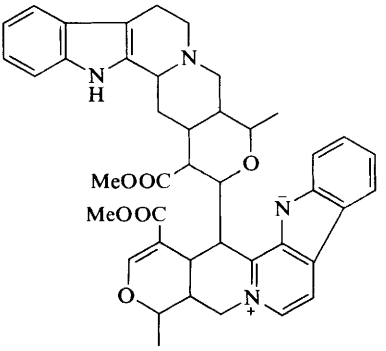
[140] E. Schlittler, H. U. Huber, F. E. Bader, and H. Zahnd, *Helv. Chim. Acta*, 1954, **37**, 1912.



B
$C_{42}H_{42}O_5N_4$



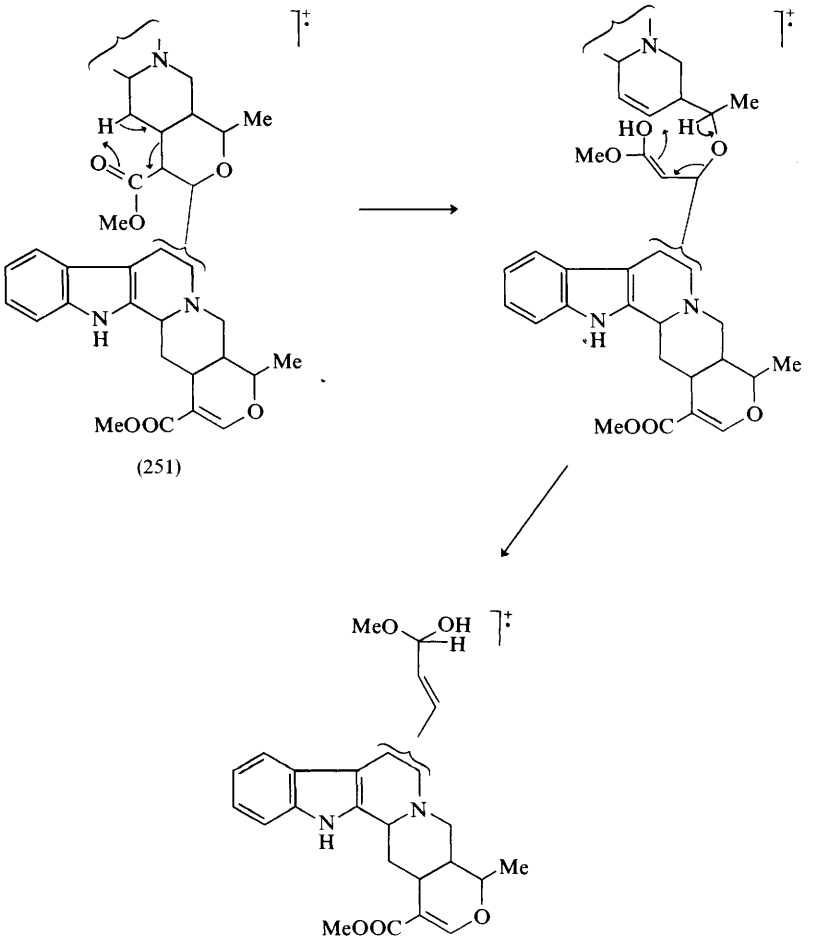
F
$C_{40}H_{38}O_3N_4$



(250)

represent addition curves of two tetrahydro-β-carboline absorptions and one β-alkoxy-acrylic ester absorption.[139] In the molecular weight region of their mass spectra two peaks at *m/e* 702 and 704 are apparent. A tetrahydroserpentinine

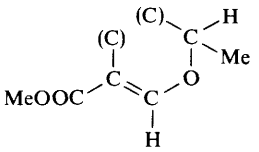
requires $M^+ = 704$.* In contrast to serpentinine itself these reduction products, particularly (251), show fragmentation peaks in their mass spectra. The first peak to be discussed, *m/e* 438 ($C_{25}H_{30}O_5N_2$), is accompanied by a peak *m/e* 437. The fragment ion 438 corresponds to the lower 'half' of (251) (or 252) plus a unit $C_4H_7O_2$ from the upper 'half'. Its depicted genesis is supported by the following deuteriation experiments:



* The compounds (251) and (252) are homogeneous on the basis of t.l.c., i.r., u.v., and in particular n.m.r. spectra. The peak *m/e* 702 is presumably a result of thermal dehydrogenation.

(*a*) In the mass spectrum of the corresponding $NaBD_4$–MeOD product ($^2H_3$-251), the peaks at *m/e* 437 and 438 are shifted to *m/e* 440 and 441.
(*b*) (251) on $NaOCH_3$–CH_3OD treatment (80 °C; 24 hr) gives a monodeuteriated product ($^2H_1$-251), in which the relevant peaks occur at *m/e* 438 and 439. The 'normal' ester function is therefore secondary.

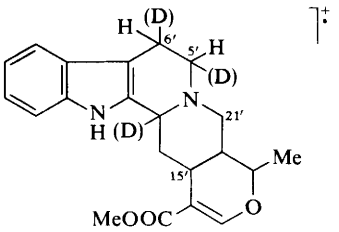
Since the β-alkoxy-acrylic ester chromophore is present in the part structure below (n.m.r. evidence, see later), it follows that the fragment ion *m/e* 438 contains the lower reduced anhydronium base part with the β-alkoxy-acrylic ester grouping and the $C_4H_7O_2$ residue from the saturated E ring of the upper 'half'.



The mass spectrum of (251) also shows peaks at *m/e* 351 and 352 which in the spectrum of ($^2H_3$-251) are shifted to *m/e* 354 and 355. They therefore correspond to the lower (reduced anhydronium base) part of (251) and in the light of this conclusion can be formulated as *af* and *ag*. In the mass spectrum of ($^2H_1$-251) peaks at *m/e* 351, 352, and 353 are observed, which demonstrates that the peak *m/e* 352 is due to a fragment ion whose genesis involves transfer of the proton α to the secondary ester function to the lower 'half'.

The mass spectral investigation of (251) thus leads to the following structural conclusions:
(*a*) Peak *m/e* 438: the lower 'half' of (251) and of serpentinine is bound to C(17) of the upper 'half' [the formation of ($^2H_1$-251) eliminates C(16) as a possible linkage position].
(*b*) Peaks *m/e* 351 and 352: from a mass spectrometric point of view the cleavage to give *af* (*m/e* 351) is only compatible with the linkage position of the lower component being one of the C-atoms 5′,6′,15′, and 21′.

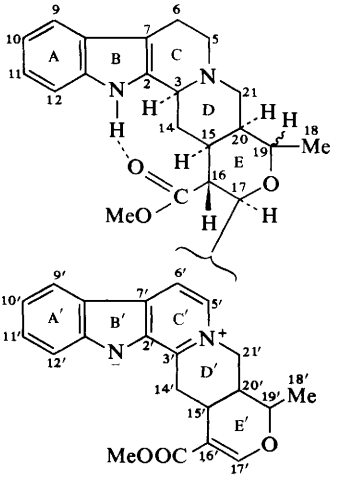
The 220 MHz n.m.r. spectrum of serpentinine in dimethyl sulphoxide shows the presence of ten aromatic protons. Amongst these signals can be recognised four



ag (*m/e* 352)
af (*ag* less H; *m/e* 351)

triplet-like doublets of doublets with $J_1 \approx 8$ Hz, $J_2 \approx 6.5$ Hz. This proves that the two benzene nuclei *A* and *A'* in serpentinine are not substituted.

In the serpentine (244) spectrum the protons at C(5) and C(6) appear in the form of doublets ($J = 6.5$ Hz) at 8.2 and 7.8 p.p.m., and that at C(17) as a singlet at 7.65 p.p.m. The serpentinine spectrum contains two one-proton singlets at 7.6 and 7.3 p.p.m., one of which must correspond to the C(17')-H, and the other to a C(5')-H or a C(6')-H. The lower unit of serpentinine must therefore be bonded from either C(5') or C(6') to C(17) of the upper component. Further signals in the serpentinine spectrum are an NH singlet at 10.75 p.p.m., methoxycarbonyl singlets at 3.3 and 3.7 p.p.m. and secondary methyl doublets at 1.2 and 1.8 p.p.m. In $CDCl_3$ serpentinine shows the NH singlet at 9.5 p.p.m. Indole



(253), Serpentinine
(251), (252), 1',3',5',6'-Tetrahydroserpentinine

alkaloids of the yohimbine and heteroyohimbine types show this signal between 7.6 and 8.1 p.p.m. and hence in serpentinine the NH function must be intramolecularly hydrogen-bonded. This hydrogen bond is broken in DMSO [NH singlet at 10.75 p.p.m. for serpentinine, 10.90 p.p.m. for ajmalicine (254)]. In the $CDCl_3$ spectrum of serpentinine one of the ten protons in the aromatic region of the DMSO spectrum, a singlet, is shifted upfield to 6.0 p.p.m. Of the stereoisomeric possibilities for serpentinine, those possessing the stereochemistry shown in structure (253) may adopt a conformation which accommodates extremely well a hydrogen bond between the indolic NH and the C(16) methoxycarbonyl group. The conformationally-fixed methoxycarbonyl group, according to models, would exert a shielding influence on the hydrogen at C(5') or C(6'). The i.r. spectrum

($CHCl_3$) of serpentinine also shows a hydrogen-bonded NH (3330 cm^{-1}); the standard NH group in heteroyohimbine types absorbs at 3445–3475 cm^{-1}.

The n.m.r. spectrum of serpentinine also exhibits a quartet-like signal at 5.85 p.p.m., shown by double resonance to correspond to the C(19)- or C(19′)-proton. This signal lies at abnormally low field. At 4.75 p.p.m. the signal of a hydrogen at C(21′) is found as a doublet of doublets, $J_1 \approx 18.5$ Hz, $J_2 \approx 4.5$ Hz. Finally, at 4.55 p.p.m. appears a multiplet corresponding to two protons, one of which is attached to C(19) or C(19′) (double resonance); in the spectrum of serpentine (244) the signals of the C(19)- and C(21)-protons appear at 4.1 p.p.m. The second signal at 4.55 p.p.m. in the serpentinine spectrum probably corresponds to the C(17)- or C(3)-proton.

In the n.m.r. spectrum ($CDCl_3$) of tetrahydroserpentinine (251) two broad NH singlets at 8.8 (intramolecular hydrogen bond) and 7.8 p.p.m. are apparent (in DMSO 10.75 and 10.55 p.p.m.). The aromatic region contains signals due to eight aromatic protons and the C(17′)-proton. One of the protons at C(19) and C(19′) again appears at low field (5.7 p.p.m.) as a quartet, the other as part of a two-proton multiplet at 4.3 p.p.m. Decoupling experiments have confirmed these assignments. The nature of the proton giving rise to the other half of the multiplet at 4.3 p.p.m. is not clear. If it is the C(17)-H, reduction of ring C′ of serpentinine has led to an upfield shift of only 0.2 p.p.m. which is difficult to understand, although on the other hand the C(17)-H in serpentinine would normally be expected to absorb in the 4—4.5 p.p.m. region.[139]

The constitution (253) proposed for serpentinine requires further confirmation.

16 Alkaloids of the Vobtusine Type

Some of the most difficult structural problems in the indole alkaloid field are associated with the bisindole alkaloids of the vobtusine type. Since 1955, vobtusine has been isolated on numerous occasions, often in large quantities, from the Apocynaceae species *Callichilia*, *Conopharyngia*, *Rejoua*, and *Voacanga*.[141,142] A correct molecular formula could only be determined by high-resolution mass spectrometry. In 1966 a partial structure was proposed[143] for the alkaloid and later in the same year a complete structure was put forward.[144] An unambiguous structural proof is, however, still lacking. The difficulty arises from the complete resistance of the alkaloid and its derivatives to cleavage, in contrast, for example, to the 'dimers' of the voacamine and vinblastine types. Non-cleavable 'dimers' occur also in calabash-curare but in these cases chemical correlation with cleavable alkaloids has been possible (see Section 2, p. 209). To date no bisindole alkaloid related to vobtusine has been found which can be split into monomeric units.

[141] J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, A. K. G. Nasser, L. Saunders, and W. B. Whalley, *Chem. Comm.*, 1966, 754.
[142] M.-M. Janot and R. Goutarel, *Compt. rend.*, 1955, **240**, 1719.
[143] J. Poisson, M. Plat, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Tetrahedron*, 1966, **22**, 1075.
[144] A. A. Gorman, V. Agwada, M. Hesse, U. Renner, and H. Schmid, *Helv. Chim. Acta*, 1966, **49**, 2072.

All the chemical reactions carried out on vobtusine have led only to modifications of the strictly 'monomeric' characteristics of the alkaloid and have given no direct information concerning the nature of the coupling between the two monomeric components. The formula of vobtusine to be discussed is supported by spectral evidence, in particular by the results of a detailed examination of the mass spectra of the alkaloid and its derivatives. Unfortunately, information to be gained from n.m.r. spectra is minimal owing to the complexity of the molecule.

A number of new alkaloids are closely related to vobtusine. These include vobtusine lactone (alkaloid V) and desoxyvobtusine lactone (alkaloid IV) from *Voacanga africana* Stapf.[145] and desoxyvobtusine, voafoline (alkaloid VII), isovoafoline, voafolidine (alkaloid IX), and folicangine (alkaloid VIII) from the same plant.[146] From *Callichilia* (*Hedranthera*) *barteri* (Hook.f.) Pichon owerreine, goziline (= desoxyvobtusine?), and amataine have been isolated.[147] All these alkaloids have been obtained in only small amounts.

The alkaloid callichiline[148] occurs in *Callichilia barteri* and *C. subsessilis* Stapf. and differs from the rest of the vobtusine group in the mode of linkage between the two 'halves'.[70,149]

Vobtusine (255).—This alkaloid, molecular formula $C_{43}H_{50}O_6N_4$,[150] shows in the i.r. spectrum an NH band and signals characteristic of the β-anilino-acrylic ester grouping which is present for example in vincadifformine (256), and the part of the vobtusine molecule containing this grouping has been denoted as part *A*. The u.v. spectrum of vobtusine represents the superimposition of vincadifformine (256) and *N*-alkyl-7-methoxyindoline spectra; the two chromophores are thus independent of each other.

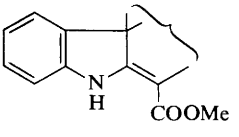
Mild nitration of vobtusine results in exclusive attack on the indoline system at position 5 (as shown by the u.v. spectrum) with the formation of nitrovobtusine (257).[70]

The complex n.m.r. spectrum of vobtusine shows signals for the NH group, two methoxy-groups, and seven aromatic protons; *C*- and *N*-methyl signals are absent. In the spectrum of nitrovobtusine (257) the signals of the two protons of the 5-nitro-7-methoxyindoline system are shifted to lower field and can be assigned with certainty to two *meta*-related protons; the chemical shifts confirm the assignment.

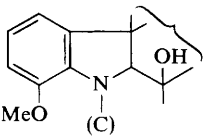
Thus, in the coupling between the two components *A* and *B* no aromatic C-atoms are involved.

[145] N. Kunesch, J. Poisson, and B. C. Das, *Tetrahedron Letters*, 1968, 1745.
[146] N. Kunesch, B. C. Das, and J. Poisson, IUPAC, 5th. International Symposium on the Chemistry of Natural Products, London, 8—13th July 1968, Abstract No. G4.
[147] V. Agwada, Dissertation, Universität Zürich 1970; V. Agwada, M. B. Patel, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1970, **53**, 1567.
[148] R. Goutarel, A. Rassat, M. Plat, and J. Poisson, *Bull. Soc. chim. France*, 1959, 893.
[149] M. Plat, N. Kunesch, J. Poisson, C. Djerassi, and H. Budzikiewicz, *Bull. Soc. chim. France*, 1967, 2669.
[150] Ref. 5, p. 8.

When heated in mineral acid vobtusine (255) gives anhydrovobtusine (258), which like vobtusine shows no vinyl proton signals in the n.m.r. spectrum. The u.v. spectrum of this product is a summation of vincadifformine (256) and 2-methylene-7-methoxyindoline spectra.* Parts *A* and *B* of vobtusine thus possess the structural elements shown.†



A



B

All chemical transformations of vobtusine have been carried out within these structural elements and the part-structures of the products formed are summarised in (257), (258), and (260)—(264). The u.v., i.r., and mass spectra of these products fully confirm the part-structures shown. The two basic $N_{(b)}$-atoms are very probably tertiary (no acetylation) and the two remaining oxygens are, on the basis of i.r. evidence, present as ether linkages. These ether linkages are resistant to lithium aluminium hydride and zinc in hot sulphuric acid.

The complete structural proposals for the two monomer components and for vobtusine itself are based almost entirely on a mass spectrometric investigation of vobtusine‡ and the derivatives already mentioned.

Part B: This is structurally related to the co-occurring *Callichilia* 'monomer' beninine (259) whose principal modes of mass spectral breakdown are shown; these are characteristic of alkaloids of the aspidospermine type.[151]

Part *B* in 2,3,2′,3′-tetrahydro-anhydrovobtusine (260) and the demethoxycarbonyl product (261) corresponds very closely to beninine (259). In the spectrum of both (260) and (261) the fragments *ai*, *ak* (also apparent in the mass spectra of vobtusine and all derivatives), *al* (R = Me), and *am* (R = Me) are observed. The last two fragments indicate that a CH_2 group is attached to $N_{(a')}$. The absence of an $(M^+ - 28)$ peak, and of the corresponding metastable peak, suggests that the $-CH_2(3')-CH_2(4')-$ bridge in the 'dimer' is bound to part *A*. These two atoms are found in the $(M^+ - 138)$ fragment of anhydrovobtusine (258) and the derivatives (262) and (263) which all possess a 2′,3′-double bond. This ion *an* occurs at *m/e* 562 for (258), *m/e* 504 for (262),§ and *m/e* 506 for (263). The fragmentation

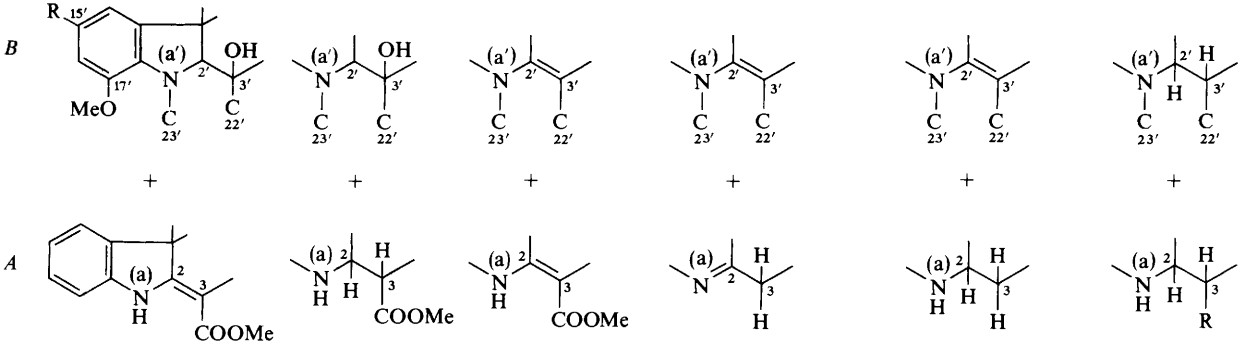
[151] Ref. 5, p. 98.

* The alternative *N*-vinyl-7-methoxyindoline chromophore is excluded on other grounds (see later).

† The failure of part *B* to react with lithium aluminium hydride indicates that the hydroxy-function is not part of a carbinolamine system.[143]

‡ All fragment ions which will subsequently be referred to have been subjected to accurate mass measurement.

§ This peak also occurs in the mass spectrum of vobtusine since the latter is partly converted thermally to (262) in the mass spectrometer.



(255), R = H; Vobtusine
(257), R = NO_2; 15′-Nitrovobtusine

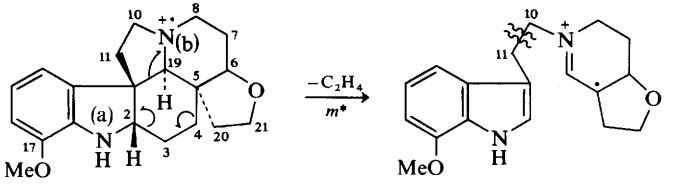
(264), 2,3-Dihydrovobtusine

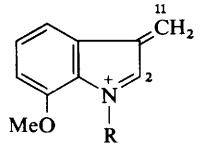
(258), Anhydrovobtusine

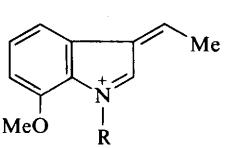
(262), Demethoxycarbonylanhydrovobtusine

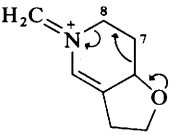
(263), Dihydrodemethoxycarbonylanhydrovobtusine

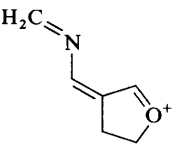
(260) R = CO_2Me; 2,3,2′,3′-Tetrahydroanhydrovobtusine
(261) R = H; Tetrahydrodemethoxycarbonylanhydrovobtusine





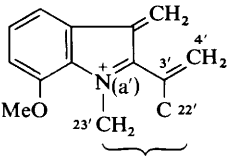


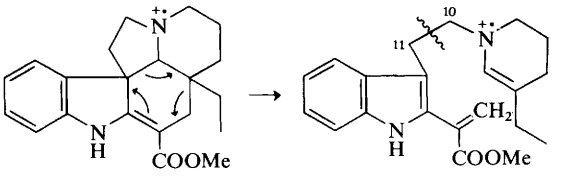




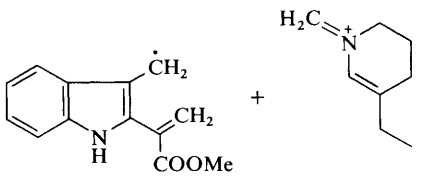
process leading to these ions is characteristic of α-methylene-indolines of the aspidospermine type as shown for vincadifformine (256).

In the mass spectrum of the demethyl derivative [phenolic OH at C(17′)] of demethoxycarbonylanhydrovobtusine (262) the fragments *al*(R = Me), *am* (R = Me) and *an* are shifted by −14 m.u.;[144] in the spectra of vobtusine lactone (270) and desoxyvobtusine lactone (271) (see Section 16, p. 305) fragment *ai* is shifted by +14 m.u.[145]





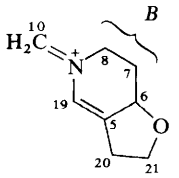
(256), Vincadifformine



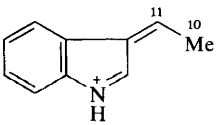
214 m.u. *ao*, *m/e* 124 (= $M^+ - 214$)

Part A: Vincadifformine (256),[152] which gives the fragment ($M^+ - 214$) (*ao*), serves well as a model for the fragmentation of part *A*. The corresponding fragment is observed in the spectra of both vobtusine (255) and anhydrovobtusine (258). The formulation of the fragment as *ap* arises from the assumption that, as in part *B*, the ether oxygen is part of a five-ring ether system. As in the case of 2,3-dihydrovincadifformine, the 2,3-dihydro-derivatives of vobtusine [(260) and (264)] lose 216 m.u. to give *ap*.

A peak due to fragment *aq* is observed in the spectra of compounds (260) and (261). This must be derived from part *A* and no longer contains C(3), thus showing that C(10) and C(11) are not substituted. The fragment *am* (R = Me) shows that the same applies to C(11').



ap, $M^+ - 214$ or $M^+ - 216$

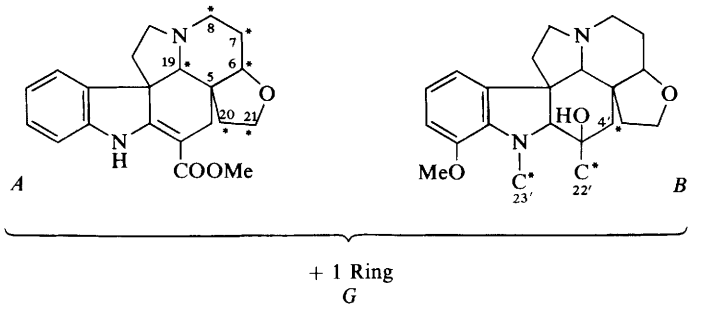


aq, *m/e* 144

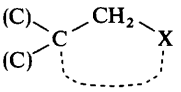
The evidence discussed so far allows a partial structure *G* to be proposed for vobtusine in which the possible positions of linkage between the two components are starred.

[152] C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. Le Men, and M.-M. Janot, *Tetrahedron Letters*, 1962, 235.

The n.m.r. spectrum of vobtusine (255) shows only one feature which yields information concerning the linkage between the two halves. This is a one-proton doublet at 5.13 p.p.m. (J = 14 Hz) which is coupled to a second doublet



at 3.09 p.p.m.[143] The nature of this AB system suggests the partial structure:



(X = N or O).

In the spectrum of anhydrovobtusine (258) the signal at 5.13 p.p.m. is shifted upfield to 4.38 p.p.m.

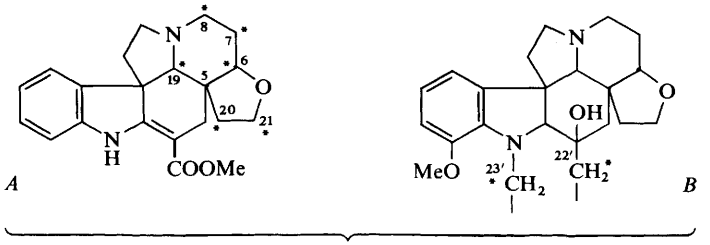
The ring structures of parts *A* and *B* shown in part formula *G* account for all but two of the vobtusine carbon atoms. From the previously discussed mass spectral data [fragment ions *al* and *am*(R = Me)], C(23′) must be one of these and on biogenetic grounds the second can only be attached to C(3′),* *i.e.* C(22′) and C(23′) in *G* do represent the two unspecified carbon atoms of vobtusine.

From part structure *G* and the possible positions of linkage it is clear that the CH_2 group in the above part structure can only be one of the atoms C(8), C(21), or C(23′), since only these of the atoms bonded to N or O could be adjacent to carbons involved in the linkage. In addition, the final ring of vobtusine must be formed by both C(22′) and C(23′) being bonded to part *A* (otherwise the above part structure could not be formed), thus automatically excluding C(4′) as a linkage position. The part structure of vobtusine is therefore extended to *H* in which either:

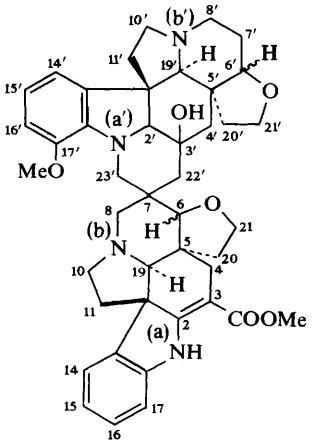
a) C(22′) and C(23′) form a spiran linkage to C(7), C(8), C(20), or C(21),
or
b) C(23′) is attached to C(6) or C(19) and C(22′) to one of the remaining starred carbon atoms in *H*.

Reasoned argument cannot develop the structure of vobtusine further than this. However, two structures, (265) and in particular (255), allow a very ready interpretation of the mass spectral fragmentation of vobtusine and its

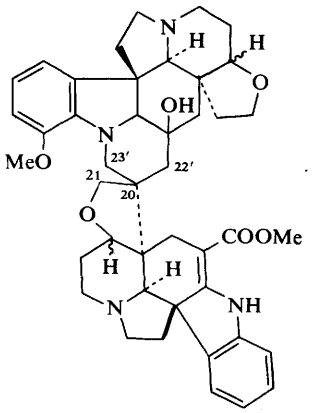
* The biogenetically plausible attachment of a two-carbon unit to $N_{(a')}$ cannot be rigorously excluded, but is incompatible with mass spectral data.



derivatives which concerns the linkages between the two components. There are two such modes of fragmentation, leading in the case of vobtusine to ions *m/e* 363 and 393, which shall be referred to as fragments F_A and F_B respectively. Comparison of the variation in mass number of these fragments in the spectra of



(255), Vobtusine



(265)

the various vobtusine derivatives (Table 3) shows that F_A is derived principally from part *A*, F_B from part *B*. The genesis of these fragments will be discussed in terms of structure (255) for vobtusine. Unless otherwise stated an entirely analogous mechanism exists in the case of (265).

The much greater intensity of the fragment F_A peak in the spectra of compounds possessing a 2',3'-double bond [(264) dehydrates very readily in the mass spectrometer] suggests that the formation of this fragment commences with decyclisation of ring C' as shown for dihydrodemethoxycarbonylanhydrovobtusine (263) in Scheme 19. This is confirmed by the presence in all spectra of a metastable peak showing the breakdown of the $M^+ - 138$ ion into the corresponding F_A fragment.

Table 3

Compound	*Fragment* F_A	*Fragment* F_B
Vobtusine (255)	363, $C_{22}H_{23}O_3N_2$ (5%)	393, $C_{24}H_{29}O_3N_2$ (20%)
2,3-Dihydrovobtusine (264)	365, $C_{22}H_{25}O_3N_2$ (35%)	393, $C_{24}H_{29}O_3N_2$ (4%)
Anhydrovobtusine (258)	363, $C_{22}H_{23}O_3N_2$ (12%)	375, $C_{24}H_{27}O_2N_2$ (6%)
Demethoxycarbonyl-anhydrovobtusine (262)	305, $C_{20}H_{21}ON_2$ (44%)	375, $C_{24}H_{27}O_2N_2$ (2%)
Desmethyl-demethoxycarbonyl-anhydrovobtusine	305, $C_{20}H_{21}ON_2$ (25%)	361, $C_{23}H_{25}O_2N_2$ (2%)
Dihydro-demethoxycarbonyl-anhydrovobtusine (263)	307, $C_{20}H_{23}ON_2$ (68%)	375, $C_{24}H_{27}O_2N_2$ (2%)
2,3,2′,3′-Tetrahydro-anhydrovobtusine (260)	365, $C_{22}H_{25}O_3N_2$ (9%)	377, $C_{24}H_{29}O_2N_2$ (37%)
Tetrahydro-demethoxycarbonyl-anhydrovobtusine (261)	307, $C_{20}H_{23}ON_2$ (16%)	377, $C_{24}H_{29}O_2N_2$ (33%)

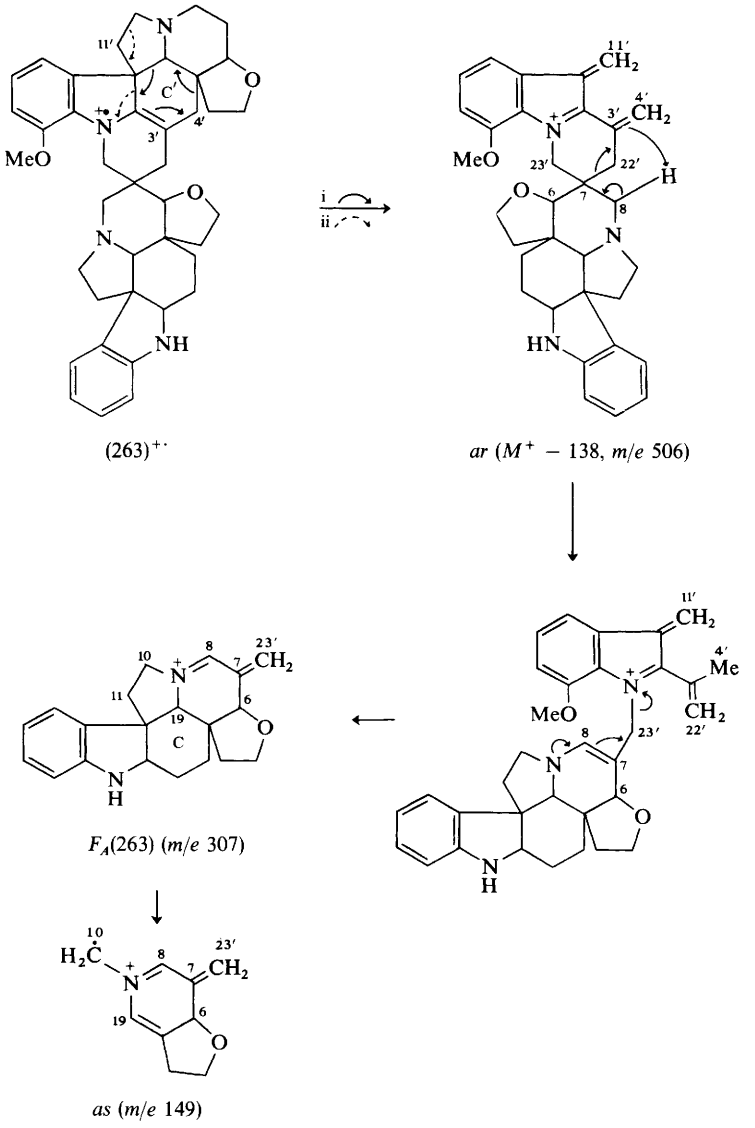
The actual process is visualised as involving a hydrogen transfer from C(8) to C(4′) followed by charge transfer from $N_{(b)}$ to $N_{(a')}$. Hydrogen migration from C(6) and charge transfer from oxygen to $N_{(a')}$ is an equivalent process. In the formation of F_A from 2′,3′-saturated compounds the hydrogen transfer reaction results in loss of propene.

The spectra of all vobtusine derivatives show a peak at *m/e* 149 ($C_9H_{11}ON$) which is intense in those spectra in which the F_A peak is intense. This is in accord with the further fragmentation of F_A to *as* by the 'normal' aspidospermine-type opening of ring C followed by C(10)–C(11) bond cleavage. The formation of *as* is an indication that part *A* contains the same tetrahydrofuran ring as part *B* and virtually eliminates C(19) as a possible position of linkage. The hydrogen and charge transfers from part *A* to part *B* necessary to form F_A are extremely difficult to accommodate with a hetero-atom relationship other than that shown in (255) and (265).

The fragment F_B is more abundant in the absence of a 2′,3′-double bond and is considered to arise from initial 'normal' opening of ring C followed by C(10)–C(11) cleavage to give *at* in the case of vobtusine itself (Scheme 20). Hydrogen migration from C(23′) to C(19) followed by charge transfer from $N_{(a')}$ to $N_{(b)}$ results in fragment F_B.

The formation of a fragment containing part *B* plus two ring-carbon atoms from part *A* strongly suggests that C(22′) and C(23′) are attached to one, or to one each of two adjacent carbon atoms of part *A* which are readily extruded from the part *A* skeleton. Of the starred atoms in *H* only the pairs C(7)–C(8) and C(20)–C(21) need seriously be considered. Given this, the n.m.r. evidence demands a spiran structure; given a spiran structure the mass spectral evidence demands the alternative structures (255) or (265).

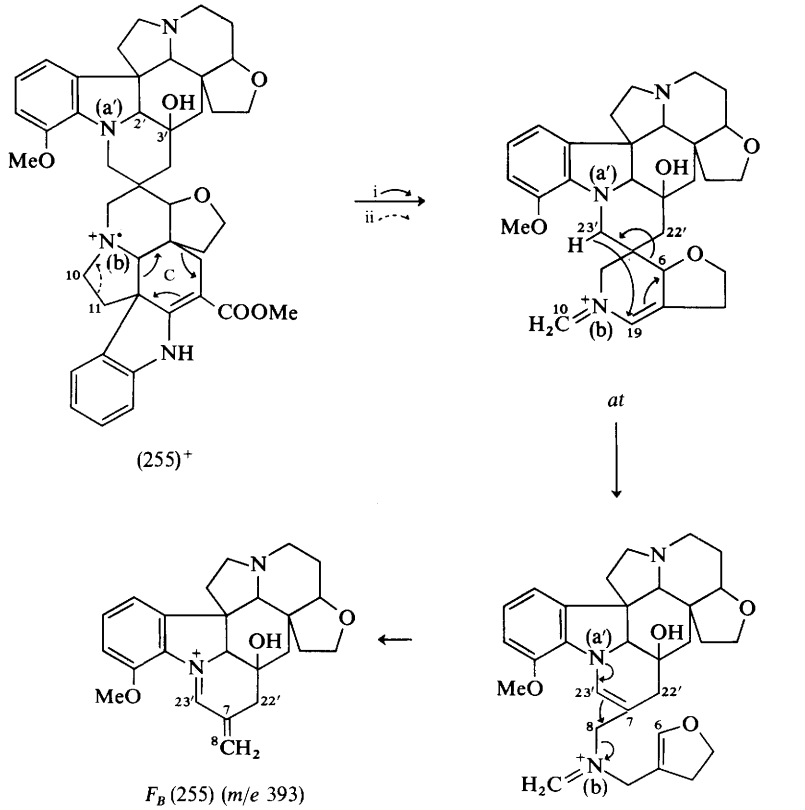
The structures (255) and (265) are also biogenetically plausible since C(22′) and C(23′) must always be electrophilic, C(7) and C(20) always nucleophilic.



Scheme 19

The formation of fragment F_B is much more difficult to rationalise on the basis of (265) than it is for (255) (Scheme 20). Hence structure (255) is preferred.

The preference for (255) is supported by o.r.d. measurements. Since alkaloids possessing indoline chromophores exhibit only very weak Cotton effects, the



Scheme 20

o.r.d. curve of vobtusine should be determined almost exclusively by the environment of the β-anilino-acrylic ester chromophore. The o.r.d. curve of vobtusine is in fact extremely similar to that of (−)-vincadifformine (256) and part *B* must therefore exert very little effect on the chromophore of part *A*. In (255) this chromophore is shielded from part *B* by the ring system of part *A*. In (265) this is not the case. The absolute stereochemistry of part *A* of vobtusine is therefore that depicted in (255). Since it has been shown by o.r.d. comparison that the co-occurring monomer beninine (259), which corresponds closely to part *B* of vobtusine (255), has this same absolute stereochemistry, it can be safely assumed that this also represents the absolute configuration of part *B*.

It is to be emphasised that to date no conclusive proof of structure (255) for vobtusine has been presented and it must be regarded as a working hypothesis.

Several bisindole alkaloids are known which are closely related to vobtusine. One monomeric unit, part *A* of vobtusine, is common to all and their mode of

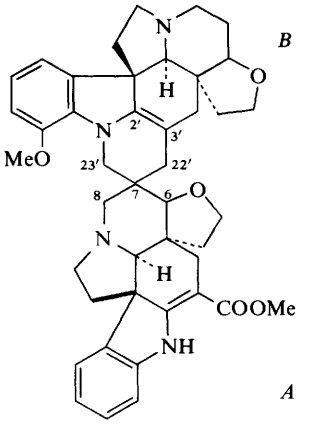
linkage is identical to that in vobtusine. With respect to the second monomeric unit, part *B*, they fall into three distinct groups.

Owerreine (266), Goziline (267) (= desoxyvobtusine ?), and Amataine (269).— These alkaloids differ from vobtusine (255) only in the oxidation level of the six-membered ring involved in the linkage between the two components.

Owerreine (*266*). The crystalline alkaloid, $C_{43}H_{48}O_5N_4$, isolated in trace amounts from *Callichilia barteri*[147] shows spectral properties which are very similar to those of anhydrovobtusine (258), the non-crystalline dehydration product of vobtusine (255). The two bases, however, run quite differently on t.l.c. and there is no doubt that the two substances are not identical. It is certain that owerreine (266) is a stereoisomer of anhydrovobtusine (258); the virtually superimposable u.v. spectra suggest that the aromatic methoxy-function is again at C(17′). The lack of material has prevented a chemical examination of owerreine.

Goziline (= *desoxyvobtusine* ?) (*267*). Although a direct comparison is lacking, it would appear that goziline from *Callichilia barteri*[147] and desoxyvobtusine from *Voacanga africana*[146] are either identical or stereoisomeric with each other.

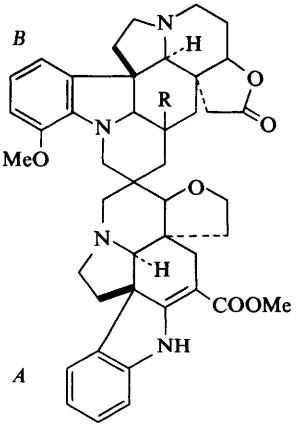
Catalytic hydrogenation of anhydrovobtusine (258) in ethanol gives amorphous *cis*-2′,3′-dihydro-anhydrovobtusine (268). That the 2′,3′-double bond has been reduced is clear from u.v., i.r., and mass spectra. Although this product shows distinctly different chromatographic properties from goziline (267), the close similarity of their spectra shows that they must indeed be stereoisomers.



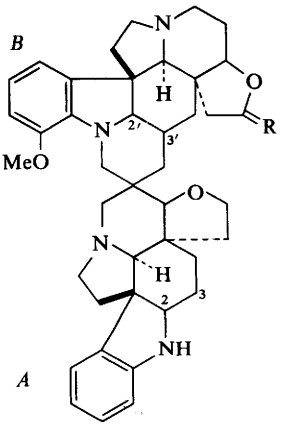
(258) Anhydrovobtusine
(266) Owerreine
(267) 2′,3′-dihydro; Goziline
(268) *cis*-2′,3′-dihydro

Amataine (*269*) (= *Grandifoline*). This alkaloid, $C_{43}H_{48}O_6N_4$, has been isolated from *Callichilia barteri* and *Voacanga grandifolia* Mig. Although a complete structural elucidation awaits further results, amataine is known to be a vobtusine derivative in which two carbons of the central six-membered ring are linked by an ether function.[147]

Vobtusine Lactone (270) and Desoxyvobtusine Lactone (271).—These bases differ from the previously described vobtusine relatives in that instead of a five-ring ether function in part *B* they contain a γ-lactone. Both alkaloids exhibit u.v. spectra identical to that of vobtusine (255). In the i.r. spectrum the β-anilino-acrylic-ester bands as well as a band at 1795 cm^{-1}, typical of a γ-lactone are apparent.



(270), R = OH
(271), R = H



(272), R = O
(261), R = H_2

The mass spectra of the two alkaloids are the same in character as that of vobtusine, but show certain shifts. In particular the fragment *ai*, *m/e* 138 in the vobtusine spectrum, in both cases appears at *m/e* 152, showing that the lactone ring is present in part *B* of the 'dimers'.

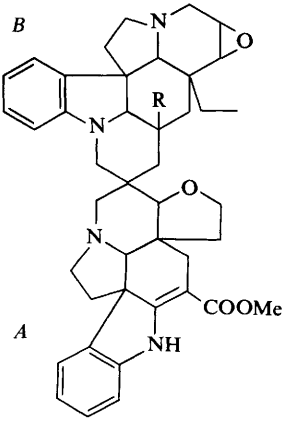
Acid-catalysed dehydration and demethoxycarbonylation of vobtusine lactone (270) followed by zinc–acid reduction gives the lactone analogue (272) of tetrahydrodemethoxycarbonylanhydrovobtusine (261). Lithium aluminium hydride reduction of the lactone ring in (272) gives a diol which on HBr treatment gives tetrahydrodemethoxycarbonylanhydrovobtusine (261). This conversion confirms that the ether ring in part *B* of vobtusine (255) is five-membered.

Demethoxycarbonylation and zinc–acid reduction of desoxyvobtusine lactone (271) gives a stereoisomer of (272) which can be converted, *via* a stereoisomeric diol, to a stereoisomer of (261).

There exist, therefore, two stereoisomeric series which we shall call the vobtusine and the isovobtusine series. Since the alkaloids of the isovobtusine series exhibit o.r.d. (owerreine and goziline) or c.d. (desoxyvobtusine lactone) curves

similar to the vobtusine series it is probable that the stereochemistry of part *A* is the same. The fact that owerreine (266) is stereoisomeric with anhydrovobtusine (258) eliminates C(2′) and C(3′) as possible isomeric centres. From work on amataine (269)[147] it appears that inversion of the spiran centre C(7) is the cause of this stereoisomerism.

Voafoline (273), Isovoafoline (274), Voafolidine (275), and Folicangine (276).—This group is characterised by the presence of an ethyl group and an epoxide function in part *B* of the 'dimers' and the absence of the aromatic methoxy-function.[146] Mass spectral and n.m.r. data coupled with chemical reactivity typical of the epoxide function lead to these conclusions. Again two stereoisomeric series are found [(273) and (274)]. The relationship of voafolidine (275) to folicangine (276) would appear to parallel that of vobtusine (255) to amataine (269).



(273), R = H; Voafoline
(274), R = H; Isovoafoline
(275), R = OH; Voafolidine
(276), R = –O–; Folicangine

Callichiline (277).—This alkaloid co-occurs with vobtusine in *Callichilia barteri*[70] and *C. subsessilis* Stapf.[148] A molecular formula $C_{42}H_{48}O_5N_4$ has been established by high-resolution mass spectrometry[70,149] and is less than that of vobtusine (255) by CH_2O. The problems associated with callichiline parallel to a large degree those of vobtusine. The alkaloid is completely resistant to attempts at cleavage and cannot be acetylated, formylated, or catalytically hydrogenated. It contains no *C*-methyl groups.

As with all naturally occurring relatives of vobtusine (255), it shows in the i.r. spectrum bands characteristic of a β-anilino-acrylic ester function. The monomeric component containing this grouping is likewise denoted as part *A*. The

u.v. spectrum of callichiline is a summation of β-anilino-acrylic-ester and methoxyindoline chromophores; the exact nature of the indoline is not readily determined from subtraction spectra.

As in the case of vobtusine, callichiline under mild nitrating conditions yields a mononitrocallichiline. The u.v. spectrum and the aromatic region of the n.m.r. spectrum of this product are virtually identical to those of 15′-nitrovobtusine (257) (Section 16, p. 296) and demonstrate conclusively that nitrocallichiline (278) is a 5-nitro-7-methoxyindoline derivative. The n.m.r. spectra (CCl_4) of callichiline (277) and nitrocallichiline (278) show the >NH resonance of the β-anilino-acrylic ester grouping at 8.98 and 8.99 p.p.m. respectively. In the spectrum of the nitro-compound an additional exchangeable proton has moved downfield to an observable position at 4.60 p.p.m. This signal can only be due to an NH function belonging to the nitrated methoxyindoline system of part *B*. Confirmation of this has been obtained from the mass spectra of deuteriated callichiline derivatives (see later).

The more important derivatives of callichiline (277) are summarised in the part structures (277)—(283). In contrast to vobtusine (255), acid treatment of callichiline gives only demethoxycarbonylcallichiline (279), no dehydration occurring. Demethoxycarbonylcallichiline (279), in contrast to demethoxycarbonylanhydrovobtusine (262), gives two products on borohydride reduction, a dihydrodemethoxycarbonylcallichiline (280), an indoline-methoxyindoline, and isodihydrodemethoxycarbonylcallichiline (281), an indole-methoxyindoline, formed *via* the well-known retro-Mannich reaction of 1,2-dehydroaspidospermidine derivatives. Demethoxycarbonylanhydrovobtusine (262) gives only the normal dihydro-product (263) (see Section 16, p. 296).

The remaining two oxygen atoms of callichiline (277) must, because of their resistance to acylation and spectral evidence, be present as ether functions. Their resistance to both lithium aluminium hydride and zinc–acid treatment excludes X–C–X linkages (X = O or N).

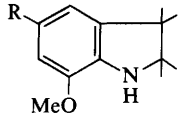
The elucidation of further structural details of callichiline depends almost entirely on mass spectral data. The mass spectrum of the alkaloid, like that of vobtusine (255), shows peaks due to the fragments *ai*, *ak*, and $M^+ - 214$ (*ap*), indicating that callichiline contains a 'beninine (259)-half' and a 'vincadifformine (256)-half'.

Since callichiline possesses one carbon less than vobtusine (255) either C(22′) or C(23′) of the latter must be missing from the former. In addition, since $N_{(a')}$ carries a hydrogen in callichiline the missing carbon is C(23′). Assuming the presence of a five-ring ether in part *A*, which will be referred to later, the part structure of callichiline can thus be extended to *I*, in which only starred atoms can be involved in bonding between the two components.

C(10) is eliminated as a linkage position owing to the appearance of the fragment *aq* (*m/e* 144) in the mass spectra of (280) and (282).

The mass spectrum of callichiline shows no peak, and no associated metastable peak, for a fragment corresponding to *ah*, which is observed in the case of beninine (259). In addition, fragments *al* and *am* (R = H) are not observed. This is only

B



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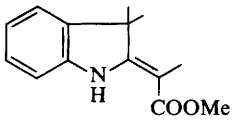
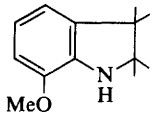


(277), R = H; Callichiline
(278), R = NO_2; Nitro-callichiline



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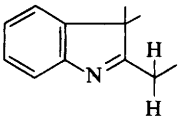
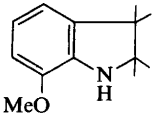


(279) Demethoxycarbonyl-callichiline



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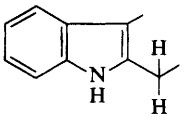
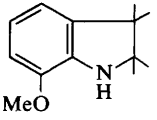


(281) Isodihydrodemethoxy-carbonylcallichiline



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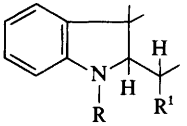
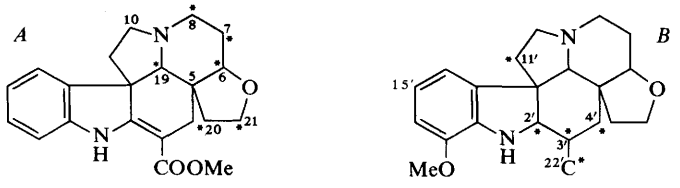


(282), R = H, $R^1 = CO_2Me$; 2,3-Dihydrocallichiline
(280), R = R^1 = H; Dihydro-demethoxycarbonylcallichiline
(283), R = CHO, R^1 = H



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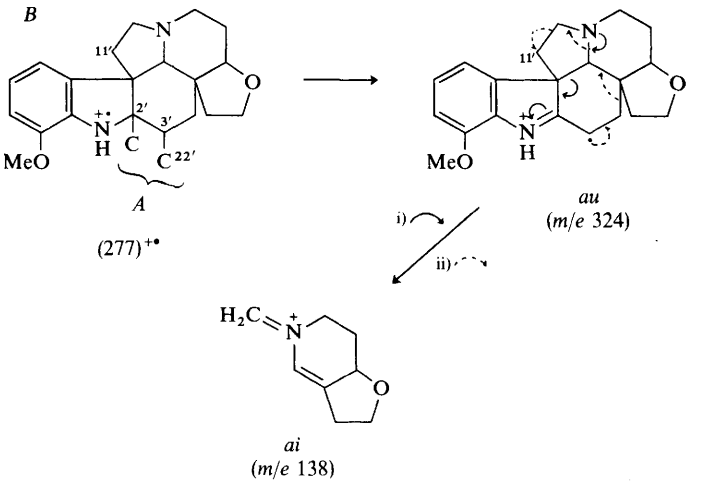
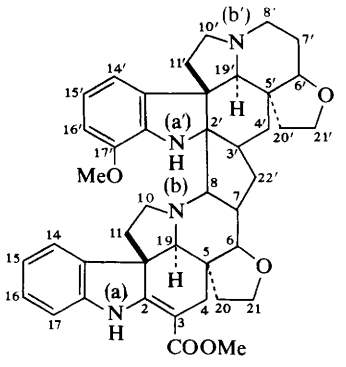
consistent with a structure in which C(2′) or C(11′) is bound to part *A*. The remote possibility that C(2′) or C(11′) is bound to C(22′) is excluded by the existence of an intense peak in the spectra of callichiline and its derivatives (15′-substituted products show the appropriate shift) at *m/e* 324. This peak corresponds to part *B* without C(22′) and containing a double bond, *i.e.* it is a dehydrobeninine ion radical (*au*). A metastable ion at *m/e* 58.8 shows that this fragment breaks down further to give the ion *ai* (Scheme 21). That C(22′) is readily lost with part *A* to give *au* shows that it cannot be doubly bound to part *B*. In addition, the formation of *au* and the further fragmentation to *ai* makes C(11′) a very unlikely candidate for a linkage position. It would appear therefore that C(2′) and C(22′) are involved in linking part *B* to part *A*.

That C(2′) is fully substituted in callichiline is supported by (*a*) the resistance of $N_{(a')}$ to formylation in all callichiline derivatives; (*b*) the sharp singlet character of the $N_{(a')}$-H signal in the n.m.r. spectra of callichiline (277) and 15′-nitrocallichiline (278) in dimethyl sulphoxide.

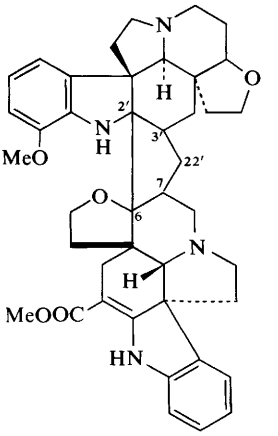


Scheme 21

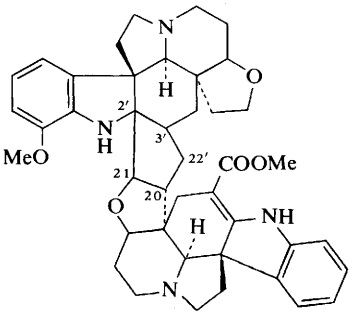
On the basis of the following mass spectral arguments it has been proposed that C(2′) and C(22′) of part *B* of callichiline are bound to part *A* in one of the ways depicted in structures (277), (284), and (285).[70] No real distinction can be made between these alternatives, although by analogy with vobtusine (255), (277) is preferred. The arguments are thus outlined with reference to the latter.



(277), Callichiline



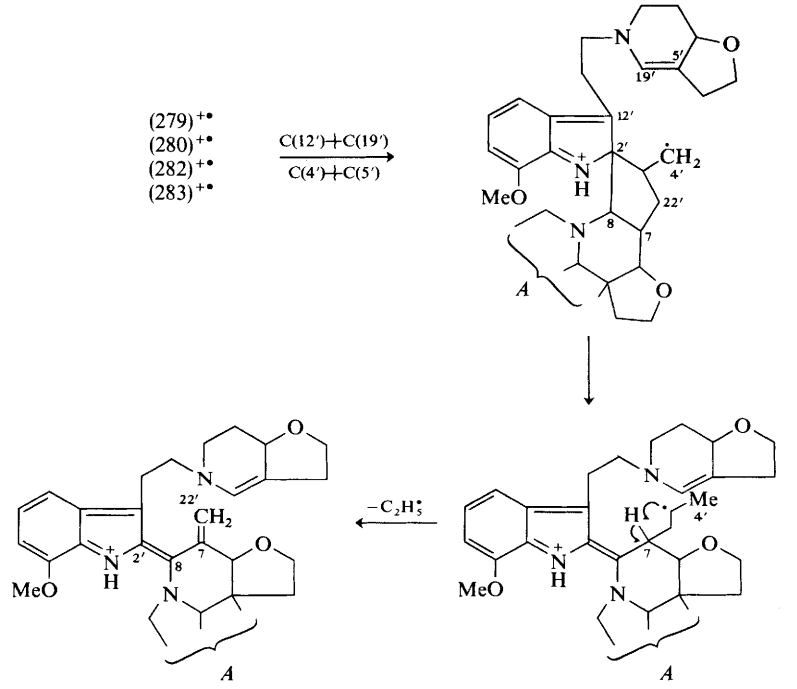
(284)



(285)

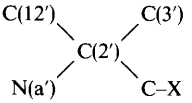
(*a*) A most interesting feature of the mass spectra of the derivatives (279), (280), (282), and (283) is the presence of an intense $M^+ - C_2H_5$ peak, in spite of the fact that n.m.r. spectra and Kuhn–Roth analyses show that callichiline and the above derivatives contain no *C*-methyl groups! Thus, the two-carbon fragment lost must originate from part of an alicyclic ring in the molecular ion. Since beninine (259), vobtusine (255), and all vobtusine derivatives show no such peak the loss of C_2H_5 must be connected with the nature of the 'dimeric' linkage. The

abundance of this ion is greater in the case of 2,3-dihydro-derivatives, indicating that fragmentation in part *B* is the primary step of its genesis. The cleavage of the C(12′)–C(19′) bond, typical of aspidospermine alkaloids, usually leads to fragments corresponding to *al* and *am* (Section 16, p. 297) (charge on the indoline nitrogen). In the case of (277) rearrangement *via* hydrogen migration can give a stable cyanine-like ion (Scheme 22), which can on further hydrogen migration lose



Scheme 22

$C_2H_5^\bullet$ to give *av*.* The formation of such a fragment indicates the presence of the unit



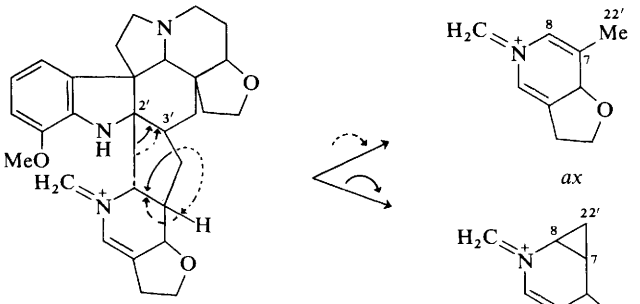
(X = N or O)

and supports the conclusion that C(2′) is fully substituted.

* Metastable peaks are observed for the process $M^+ \rightarrow M^+ - C_2H_5$ for (279) (*m/e* 573.9), (280) (575.8), (282) (633.4), and (283) (603.5).

(*b*) There are two mass spectral processes which support the previously mentioned assumption that callichiline possesses a five-ring ether in part *A* as well as in part *B*:

(*i*) Standard fragmentation in part *A* leads to the ion *aw* (*m/e* 474)* in the cases of all callichiline derivatives which are not substituted at C(15′). An intense metastable peak at *m/e* 47.4 shows that *aw* breaks down directly to a fragment *m/e* 150 ($C_9H_{12}ON$) which is formulated as *ax* or *ay*. This fragment from part *A* corresponds to *ai* from part *B* plus an additional carbon atom [C(22′)].



aw
(*m/e* 474)

ax

ay
(*m/e* 150)

(*ii*) In the mass spectrum of callichiline (277) an intense peak at *m/e* 349 appears which corresponds to a fragment containing all the C, N, and O atoms of part *A*. The structure of this fragment ion (*az*) (Scheme 23) is supported by its replacement in the spectrum of 2,3-dihydrocallichiline (282) by a fragment ion *m/e* 265 (*ba*), since in the latter case decyclisation of ring C results in the loss of methyl acrylate (86 m.u.). The formation of *ba*, in which three double bonds must be introduced into the alicyclic portion of the fragment, makes the presence of a bridged ether system unlikely, thus supporting the presence of the five-ring ether shown.

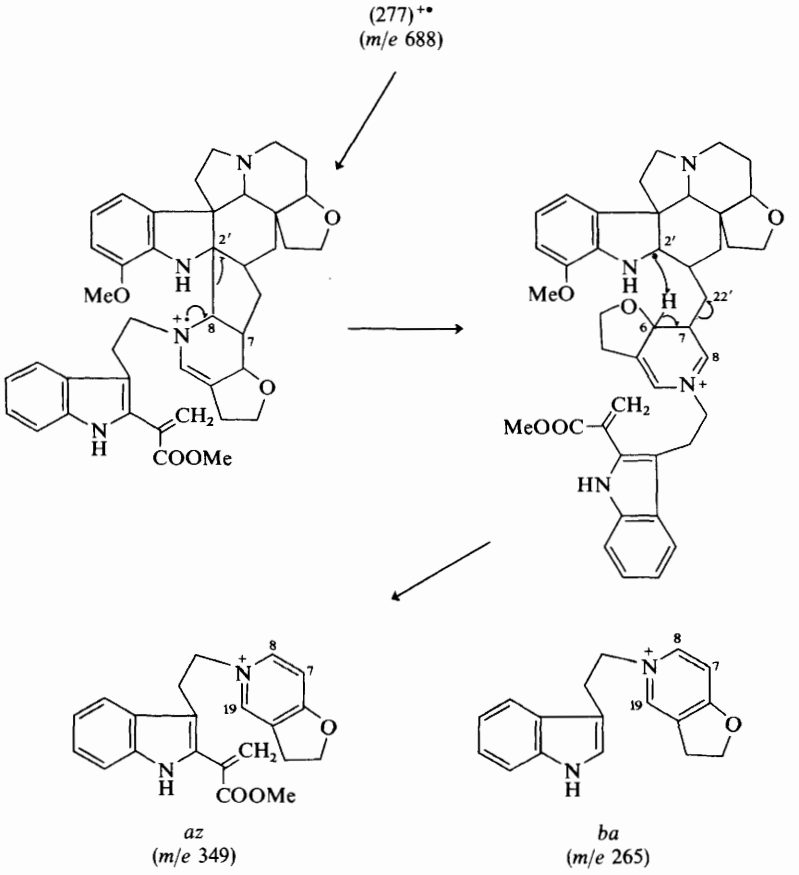
The formation of fragments *ax* or *ay*, *az*, and *ba* also excludes C(19′) as a position of linkage and is considered to exclude structures in which the points of linkage from part *A* to C(2′) and C(22′) are not in a vicinal relationship.

(*c*) From a biogenetic point of view C(22′) is a potentially electrophilic centre; of part *A* only C(7) and C(20) are potentially nucleophilic. If the vicinal relationship of the linkage positions in part *A* is assumed, alternative structures (277), (284), and (285) follow for callichiline, which all automatically include the $N_{(a')}$—C—C—X (X = O or N) unit already postulated.

(*d*) A number of deuteriated derivatives of callichiline have been prepared and their mass spectra are in agreement with the arguments which have led to alter-

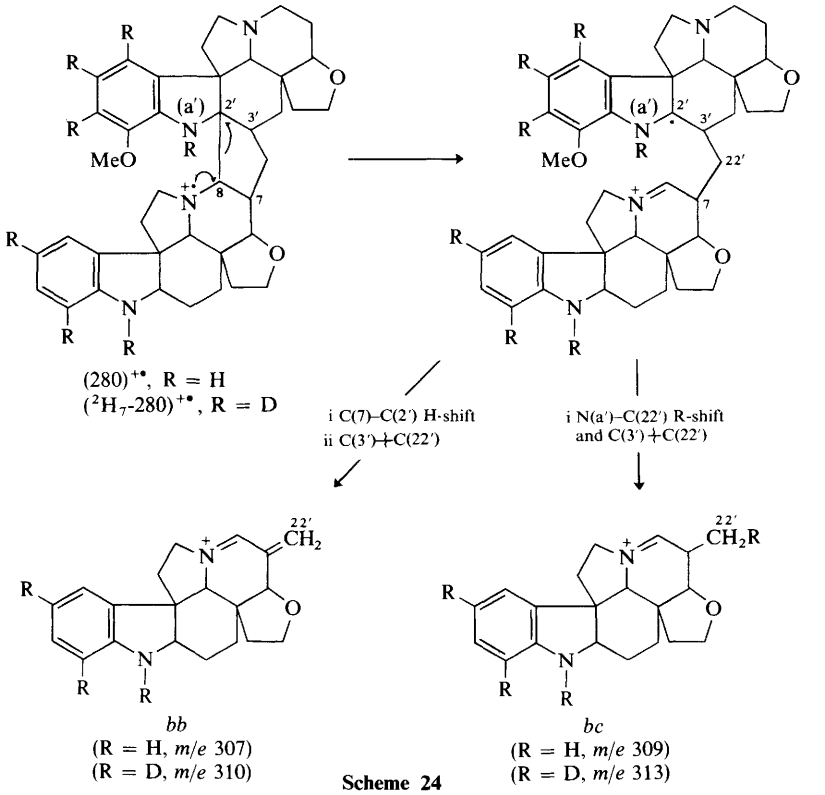
* This corresponds to *ap* in the vobtusine series (see Section 16, p. 298).

native structures (277), (284), and (285) for the alkaloid. One final piece of mass spectral evidence will be discussed in detail: two important fragments in the mass spectra of all callichiline derivatives contain all of part *A* plus C(22′). In the mass spectrum of dihydrodemethoxycarbonylcallichiline (280) these occur at *m/e* 309 and 307; the former requires hydrogen transfer from part *B* to part *A*, the latter hydrogen transfer in the opposite direction. A possible mechanism of formation of these fragments (*bb* and *bc*) is shown in Scheme 24. In the mass spectrum of the heptadeuterio-derivative ($^2H_7$-280)* the peak *m/e* 307 is shifted



Scheme 23

* The formation of the product in 3N-DCl–D_2O confirms the presence of an $N_{(a')}$-H grouping (see ref. 149).



Scheme 24

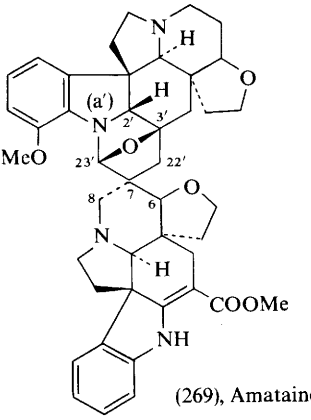
by three mass units to 310, the peak *m/e* 309 by four mass units to 313. This confirms that in the formation of the latter fragment, as shown in Scheme 24, the $N_{(a')}$-hydrogen is transferred from part *B* to part *A*.

The o.r.d. curve of callichiline is similar to that of vobtusine (255), showing that part *A* has the same absolute configuration in both 'dimers'. Likewise it is to be assumed that the configuration of part *B* is the same, *i.e.* that of the co-occurring monomer beninine (259).

In conclusion it must be emphasised that no definitive proof of the structure of any bisindole alkaloid of the vobtusine group exists. For conclusive information one perhaps awaits the *X*-ray crystallographer, although *X*-ray analysis attempts to date have proved fruitless.

Recent Developments.—It has been shown, since the completion of this manuscript, that amataine (see Section 16, p. 305) possesses the structure (269). It is the first alkaloid of the vobtusine group to be cleaved, having yielded the 1,2-dehydro-derivative of beninine (259) (see Section 16, p. 297) on treatment with phosphoric acid. In addition, the chemistry of this bisindole alkaloid has conclusively shown that the vobtusine and isovobtusine series differ only in the

configuration of the spiran centre at C(7). Amataine belongs to the isovobtusine series.[147,152a–c]



(269), Amataine

These results provide strong support for the structures proposed for vobtusine (255) and its relatives.

17 General Remarks concerning Bisindole Alkaloids

U.V. Spectra and Ceric Sulphate Reactions.—The u.v. spectrum of a bisindole alkaloid is not only important in determining the chromophoric groups present, but can be of great value in the elucidation of the alkaloid structure in a 'dimeric' sense. This naturally depends on the nature of the coupling between the two monomeric components and the positions of the individual chromophores relative to each other.

The following discussion is restricted to aromatic chromophores. Although the same applies to additional chromophores, *e.g.* the amino-acrylic-ester chromophore (roxburghines, Section 5), the alkoxy-acrylic-ester chromophore (serpentinine, Section 15), and the alkoxy-acrolein chromophore (macralstonine, Section 12, p. 269), these are as a rule readily recognised from characteristic i.r. and n.m.r. absorptions.

On the basis of their u.v. spectra, bisindole alkaloids fall into two categories. The first group consists of 'dimers' in which the two chromophores are completely isolated from each other, the second of those in which the two chromophores exert some degree of electronic interaction on each other. Each category can be divided into two sub-groups: (*a*) those in which the two 'monomeric' chromophores are identical and (*b*) those in which they are different.

[152] [a] N. Kunesch, B. C. Das, and J. Poisson, *Bull. Soc. chim. France*, 1970, 4370; [b] M. Moquet, N. Kunesch, B. C. Das, J. Poisson, V. Agwada, J. Naranjo, M. Hesse, and H. Schmid, to be published; [c] J. Naranjo, Dissertation, Zürich, in preparation.

Table 4 *Classification of bisindole alkaloids according to u.v. spectra*

Category 1
(isolated 'monomeric' chromophores)

Section	Group 1 [same 'monomeric' chromophores]	Section	Group 2 [different 'monomeric' chromophores]	
1	Calycanthine (1) Folicanthine (6) Chimonanthine (7) *meso*-Chimonanthine (8) Calycanthidine (9) Hodgkinsine (20) Quadrigemine A (27) Quadrigemine B (28)	3	Tubulosine (83) Desoxytubulosine (84) Isotubulosine (85)	Desmethyltubulosine (86) Alangimarckine (87)
2	Caracurine II Caracurine II dimetho-salt (50) *C*-Alkaloid D (53) *C*-Calebassine (55) *C*-Alkaloid F (57) *C*-Alkaloid A (52) Caracurine V dimetho-salt (39) Caracurine V (44)	6	Haplophytine (99)	
4	Cinchophyllamine (91) Isocinchophyllamine (92)	7	Geissospermine (105)	Geissolosimine (125)
5	Roxburghines D(96), A, B, C, E	8	Presecamine (138) Tetrahydropresecamine	Dihydropresecamine
8	Secamine (127) Dihydrosecamine (128) Tetrahydrosecamine (129)	9	Voacamine (141) Demethoxycarbonyl-voacamine (158) Voacamine-*N*(*b*)-oxide (159) Voacamidine (145)	Voacorine (161) 20'-Epivoacorine (162) Gabunine (165) Conodurine (166) Conoduramine (167)
		10	Vinblastine (169) Vincristine (170) Leurosidine (181) Leurosine (183)	Pleurosine (184) 'Isoleurosine' (185) Catharine (192)
		12	Villalstonine (213) Macralstonine (220)	Macralstonidine (226)
		14	Gabonine (243)	
		15	Serpentinine (253)	
		16	Vobtusine (255) Vobtusine lactone (270) Desoxyvobtusine lactone (271) Voafoline (273) Isovoafoline (274)	Voafolidine (275) Folicangine (276) Goziline (267) Amataine (269) Owerreine (266) Callichiline (277)

Category 2
(interacting 'monomeric' chromophores)

Section	Group 1 [same 'monomeric' chromophores]	Section	Group 2 [different 'monomeric' chromophores]
2	*C*-Dihydrotoxiferine (46) Bisnor-dihydro-toxiferine (48) *C*-Alkaloid H (49) *C*-Toxiferine (38) *C*-Curarine (54) *C*-Alkaloid G (56) *C*-Alkaloid E (51)	13	Pleiomutine (230) Umbellamine (235)
11	Pycnanthine (193) Pycnanthinine (195) Pleiomutinine (194)		

In Table 4 the known bisindole alkaloids are listed according to this classification.

In order to identify the chromophore of a bisindole alkaloid, it is often enough to add the spectra of the two suspected monomers [*e.g.* the u.v. spectrum of geissospermine (105) was obtained by superimposition of the spectra of an indole (cinchonamine) and an indoline (geissoschizoline)].[57] Steric constraints introduced in the dimerisation process can, of course, result in small differences in actual and manufactured spectra but these do not affect first-order interpretations. In contrast, a decision concerning the position of an auxochrome (*e.g.* 5-methoxy- or 6-methoxy-indoline ?) can certainly be jeopardised. Whenever possible such distinctions must be made by examination of the monomeric products of cleavage.

If cleavage is impossible or only one fission product may be obtained then analysis should be carried out by means of subtraction spectra. Subtraction spectra must be preferred to addition spectra since, in the latter, differences in the model chromophore and the chromophore actually contributing to the spectrum of the 'dimer' are masked, especially when the other contributing chromophore has a high extinction coefficient.

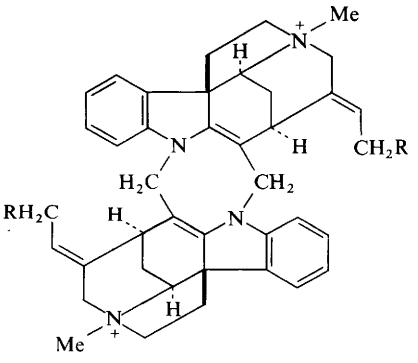
If something is known concerning a part chromophore, *e.g.* it is an NH-indoline, then for the subtraction curve an NH-indoline should be employed which is as closely related structurally to the indoline unit of the dimer as is possible (the NH-indoline cleavage product if available; if it is known to possess an aspidospermine skeleton, the spectrum of an aspidospermine rather than a *Strychnos* type should be used). The importance of such observations can be best demonstrated by the case of callichiline (277) (Section 16, p. 306). The alkaloid cannot be cleaved and its u.v. spectrum is clearly a summation of β-anilino-acrylic ester (part *A*) and indoline chromophores, the latter known to carry a methoxy-substituent. It is possible to modify the chromophore of part *A* to give the corresponding indolenine, indoline, and *N*-formyl-indoline without altering part *B*. It was known from mass spectra that part *A* possessed an aspidospermine skeleton. The u.v. spectra of echitovenine (β-anilino-acrylic ester), 1,2-dehydro-aspidospermidine (indolenine), 6,7-dehydro-aspidospermidine (indoline), and the corresponding $N_{(a)}$-formyl derivative were subtracted from the corresponding callichiline preparations. All the subtraction spectra were very similar and were averaged. Since in the spectra of NH- and *N*-alkyl-6-methoxy-indolines the ratio in intensities of low wavelength to high wavelength bands is 1.2—1.5, and in the subtraction chromophores the ratio was 2—4, callichiline (277) cannot possess a 6-methoxyindoline chromophore with either an NH- or an *N*-alkyl grouping. However, the addition spectrum of tabersonine (β-anilino-acrylic-ester; aspidospermine skeleton) and 7-methoxy-1,2,3,4,9,10-hexahydro-9,11-dimethylcarbazole (6-methoxyindoline) is practically superimposable on the spectrum of callichiline.[149] The chromophore of part *B* could only be correctly assigned from the n.m.r. and u.v. spectra of a nitrated callichiline, and was shown to be that of an NH-7-methoxyindoline.

That a monomer chromophore can change appreciably on incorporation into a 'dimer' is again demonstrated by callichiline. Part *B* of the alkaloid is the NH-7-

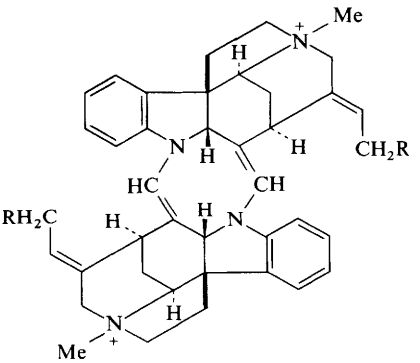
methoxy-indoline derivative beninine (259), which co-occurs with callichiline (277) in *Callichilia barteri*. The averaged subtraction spectrum of callichiline (277), λ_{max} 252 nm (log ε 3.85), 301 (3.38), although very similar in intensity, is shifted appreciably to longer wavelength compared to that of beninine (259), λ_{max} 246 (3.85), 291 (3.43).

The above discussion applies exclusively to alkaloids of the first category.

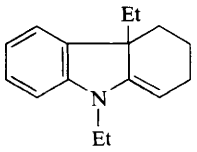
Of the alkaloids in the second category none has so far been encountered in which the chromophores of the two monomeric components are conjugated. However, homoconjugative arrangements are common. If such a situation involves two identical chromophores, it appears that to a first approximation the spectrum will be similar in character to that of the individual chromophores but both wavelengths of maxima and extinction coefficients may be appreciably increased. Analysis in these cases, however, becomes very difficult. This will be illustrated by two examples: at one time two alternative structures [(286) and (287)] were considered for *C*-toxiferine (38) and *C*-dihydrotoxiferine (46),



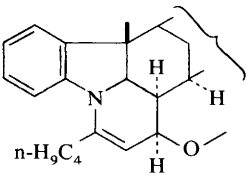
(286), R = OH
(287), R = H



(38), R = OH
(46), R = H



(288)
λ_{max} 278 nm (log ε = 4.00)



(289)
λ_{max} 286 nm (log ε = 4.04)

respectively. The α-methylene-indoline compound (288) and the 22-n-butyl-22,23-dehydrostrychnidine (289) were taken as model compounds. The u.v. curve of (288) corresponded better in shape to that of bisnor-*C*-toxiferine [λ_{max} 292 (log ε 4.62)] and on this basis the alternative structures (286) and (287)

were originally preferred. The homoconjugation in the toxiferine (38) chromophore causes not only a shift of the maximum to longer wavelength but also a strong enhancement of the extinction coefficient by a factor of 2 compared with the normal summation spectrum.

As a second example the addition curve for pycnanthine (193), the monomeric models being $N_{(a)}$-methyl-6,7-dehydrotuboxenine (206) and 2,7-dihydropleiocarpamine (197), and the actual spectrum of the 'dimer' which is distinctly different, are shown in Figure 1 (see Section 11, p. 257).

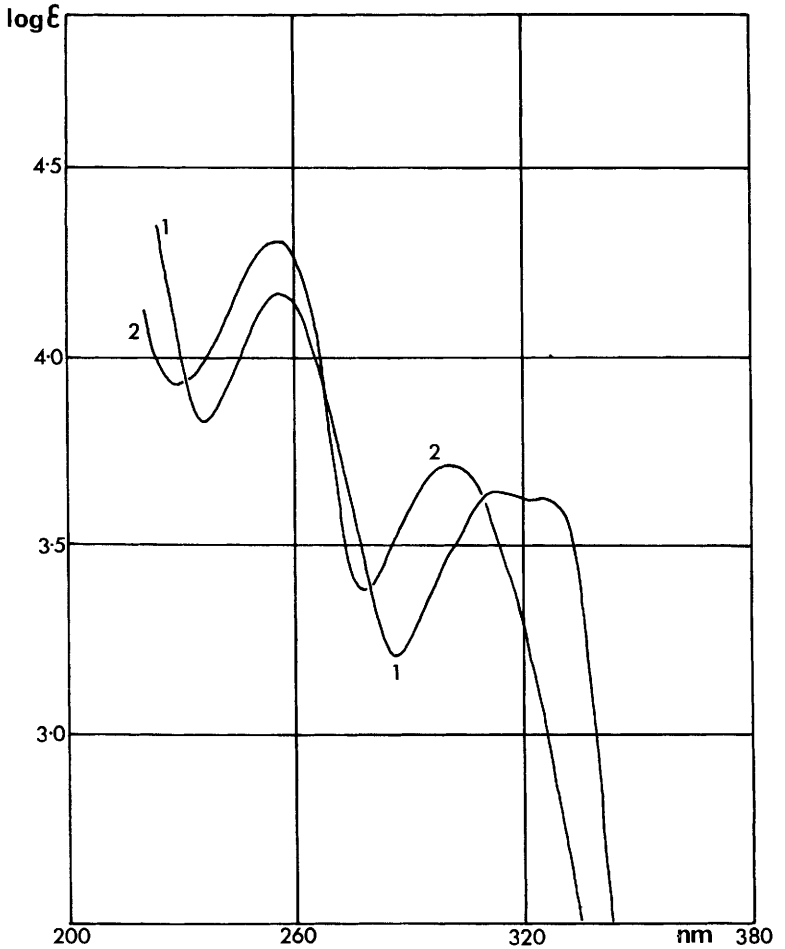


Figure 1 *Curve 1. U.v. spectrum in ethanol of pycnanthine* (193)
Curve 2. Addition spectrum of $N_{(a)}$*-methyl-6,7-dehydrotuboxenine* (206) and 2,7-*dihydropleiocarpamine* (197)

Once known, the characteristic spectra of alkaloids of the second category are of great value in the classification of new alkaloids. For instance, pycnanthinine (195), a trace alkaloid of *Pleiocarpa pycnantha*, exhibits a u.v. spectrum which is virtually identical to that of pycnanthine (193). The nature of its 'monomeric' chromophores and the mode of linkage were thus immediately clear. Two fission reactions then yielded the complete structure.

An analysis of the chromophore of the 'dimer' and 'dimeric' derivatives is a basic necessity since cleavage reactions often result in modification of one or both of the 'monomeric' chromophores present in the alkaloid itself. Such behaviour is shown by the bisindole alkaloids of the calabash-curare, presecamine, pycnanthine, *Alstonia*, and pleiomutine–umbellamine groups. Such chromophoric changes are of paramount importance in determining the mode of coupling.

In general, bisindole alkaloids show very characteristic ceric sulphate reactions. In contrast to the monomeric alkaloids (see refs. 18,19,153) there is often apparently no direct relationship between the colour reaction and the nature of the aromatic chromophore.

Pycnanthine (193) gives a red ceric sulphate reaction as do its $N_{(a)}$-alkylindoline building blocks $N_{(a)}$-methyl-6,7-dehydrotuboxenine (206) and 2,7-dihydropleiocarpamine (197). If the isolated ester function of 2,7-dihydropleiocarpamine (197) is reduced to the alcohol the ceric reaction remains red. The corresponding reduction product from pycnanthine, pycnanthinol, gives in contrast a blue-black ceric reaction.

Macralstonine (220) shows, as does its monomeric unit alstophylline (221), an intense dirty blue colour reaction—non-hydroxylated or methoxylated indoles give only a weak ceric reaction.

Toxiferine I (38), curarine (54), and their derivatives, however, give colour reactions which are specific for the 'dimer' (intense red fading to yellow and blue fading to pink respectively).

Pleiomutine (230) gives a not very characteristic brownish yellow colour reaction which fades after two days to purple, the colour of the constituent pleiocarpinine (232). Surprisingly, villalstonine (213) gives no ceric sulphate reaction.

I.R. Spectra.—In a 'dimeric' sense i.r. spectroscopy is probably the least important spectral method. The absorptions of functional groups are not affected unless they play a part in the actual linkage between components. Thus, the characteristic double ester band of the monomer 2,7-dihydropleiocarpamine (197) remains unchanged in the bisindole alkaloids villalstonine (213), pycnanthine (193), pleiomutinine (194), and pycnanthinine (195). Recognition of similarities in the i.r. spectra of 'dimers' and monomers can obviously yield information concerning constituent units. The value of such information can be enhanced by comparison of the i.r. spectrum of the 'dimer' with that of an equimolar

[153] F. Berlage, Dissertation, Universität Zürich, 1960.

mixture of the possible monomers (both spectra measured at the same molar concentration). In particular, the number of strongly absorbing functional groups (carbonyl groups, indoline systems *etc.*) can be assessed. This i.r. summation technique has been employed in the cases of vinblastine (169) and leurosine (183).[95,97]

N.M.R. Spectra.—Although the n.m.r. technique naturally remains the same for bisindole alkaloids as for the monomers, it has to be borne in mind that the resonance positions of protons in a component can be dramatically affected by shielding or deshielding influences of the other component.

First of all such effects in relatively rigid systems will be considered. It has been estimated that in the case of bisnor-toxiferine (45) (and of the toxiferines) the C(17) and C(17′) α-enamine protons experience a low-field shift of 0.4—0.5 p.p.m. owing to the anisotropy of the neighbouring benzene ring.[154] A similar situation exists within the curarine group (Section 2).[155] The strong deshielding of the C(16)-proton of alkaloids of the pycnanthine type by the ring current effect of the benzene ring of the tuboxenine (or aspidospermidine) 'half' has already been referred to (see Section 11).

Alkaloids in which the two components are joined by only one bond clearly have greater flexibility than the aforementioned doubly-bound systems. In a number of such cases, in $CDCl_3$, pronounced shielding effects by π-systems on aromatic protons [pleiomutine (230)] and methoxy-protons [voacamidine (145), macralstonine (220), and umbellamine (235)] have been observed. In $CDCl_3$ these alkaloids must therefore exist predominantly in one conformation. A change of solvent [$CDCl_3 \rightarrow (CD_3)_2SO$] can cause dramatic changes (see serpentinine, Section 15). The n.m.r. spectrum is particularly important for the establishment of the aromatic substitution pattern and the mode of coupling. A number of bisindole alkaloids possess an unsubstituted* and a doubly substituted benzene ring. With knowledge of the structure of the cleavage products, it is a simple matter to arrive at the substitution pattern of the doubly substituted benzene ring from the n.m.r. spectrum: the alkaloids of the voacamine and vinblastine types (Sections 9 and 10) as well as macralstonidine (226) (Section 12, p. 275) and umbellamine (235) (Section 13, p. 282) come into this category.

In the cases of bisindole alkaloids which possess only one substituted aromatic position the seven-proton aromatic region of the n.m.r. spectrum needs to be well enough resolved to allow analysis. At 100 MHz this is the case for alkaloids of the pycnanthine group (Section 11) and pleiomutine (230) (Section 13, p. 279). The β-carboline derivative serpentinine (253) contains ten aromatic protons and the 100 MHz spectrum yields little information; in contrast, the 220 MHz spectrum

[154] W. v. Philipsborn, Habilitationsschrift, Universität Zürich, 1962.
[155] J. Nagyvàry, W. Arnold, W. v. Philipsborn, H. Schmid, and P. Karrer, *Tetrahedron*, 1961, **14**, 138.

* The extent of substitution refers to the presence of additional substituents on the benzene ring of the indole system.

allows the aromatic substitution pattern to be restricted to two possibilities (Section 15).

In more difficult cases selective deuteriation or nitration may be employed. The former technique has been successfully employed with pleiomutine (230). The utilisation of the strongly electron-withdrawing effect of a nitro-group to spread out the aromatic proton signals and facilitate analysis is illustrated by the examples of vobtusine (255) and callichiline (277) (Section 16).

Mass Spectra.*—Because of their molecular weight the bisindole alkaloids as a general rule volatilise at higher temperatures (usually > 300 °C) than monomeric indole alkaloids. The probability of purely thermal processes taking place is thus higher. Of these, the following are relatively frequently observed:

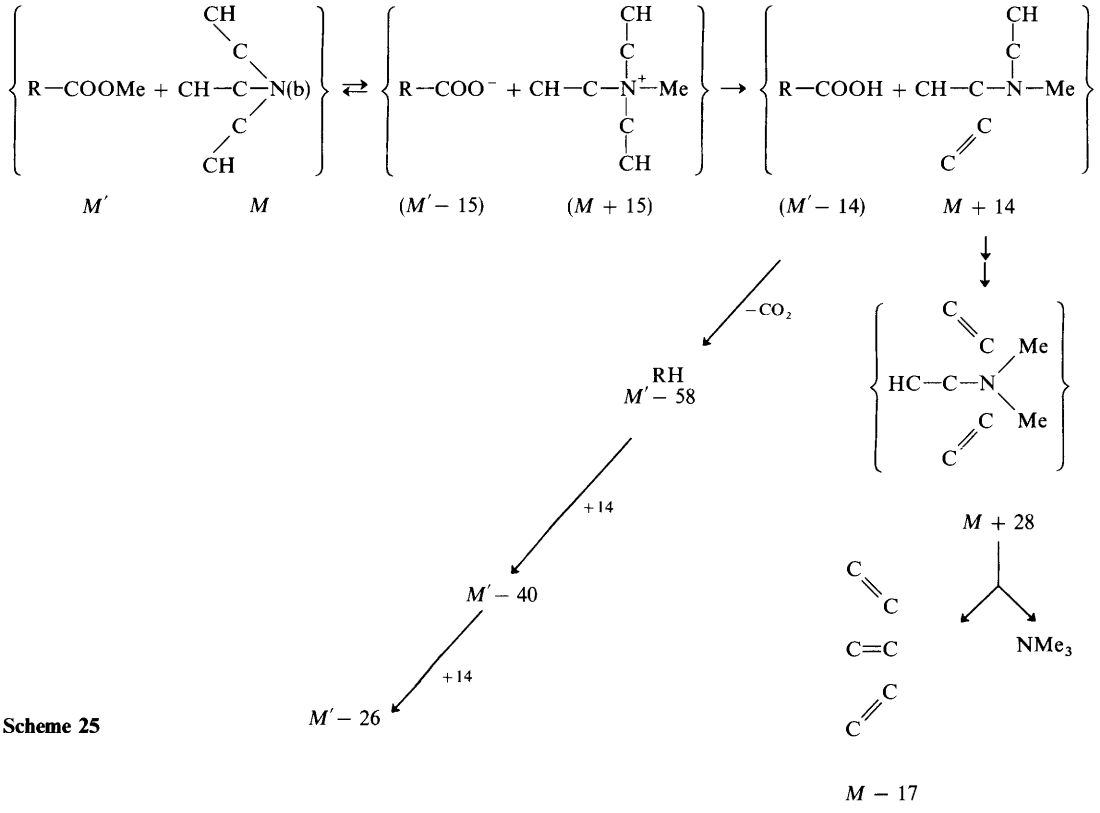
Transmethylation (*see ref. 156*). This reaction is observed with alkaloids which possess at least one methoxycarbonyl-function and a basic nitrogen atom. The process involves transfer of the methyl group from the ester to the nitrogen, whereby the quaternary ammonium salt formed can undergo Hofmann degradation, the proton abstractor being the carboxylate anion. Either inter- or intramolecular transmethylation can take place. The former requires a sterically favourable arrangement of the two reaction centres and results in ionisation of the alkaloid.

Scheme 25 summarises the molecular ions to be expected from thermal intermolecular transmethylation of a tertiary $N_{(b)}$-atom. Such reactions have been investigated with simple model compounds.[156] In the realm of bisindole alkaloids they were first observed with voacamine and vinblastine types. With the help of deuterium labelling it has been shown in the case of voacamine (141) (Section 9, p. 242) that the methyl group of the α-indolylacetic acid methyl ester function of the *Iboga* component is transferred to the $N_{(b)}$-atom of the vobasinol component.[157] An α-indolylacetic acid methyl ester is also present in the *Vinca* bisindole alkaloids (Section 10). It seems probable that the methyl transfer takes place in concert with decarboxylation to give the anion (290). The other methoxycarbonyl group is apparently not involved in methyl transfer.

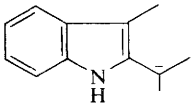
The majority of bisindole alkaloids which possess methoxycarbonyl groupings, other than of the above-mentioned type, *e.g.* villalstonine (213), pycnanthine (193), and vobtusine (255), show no significant methyl transfer in the mass spectrometer. An exception is umbellamine (235) (Section 13, p. 279). The occurrence of such reactions can be minimised by dispersion of the sample on glass powder before vaporisation,[158] thus facilitating determination of the true molecular weight. The latter may be confirmed in the case of α-indolylacetic acid methyl ester derivatives by examination of reduction or demethoxycarbonylation products.

[156] H. J. Veith and M. Hesse, *Helv. Chim. Acta*, 1969, **52**, 2004.
[157] D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, 1965, **87**, 5447.
[158] P. Bommer, W. McMurray, and K. Biemann, *J. Amer. Chem. Soc.*, 1964, **86**, 1439.

* *cf.* ref. 92.


R—COOMe + CH—C—N(b)
CH
C
C
CH
R—COO⁻ + CH—C—N⁺—Me
R—COOH + CH—C—N—Me
M′
M
(M′ − 15)
(M + 15)
(M′ − 14)
M + 14
−CO₂
RH
M′ − 58
+14
M′ − 40
+14
M′ − 26
HC—C—N
Me
M + 28
NMe₃
C=C
M − 17

Scheme 25



(290) (M − 59)

Retro-Diels–Alder Reactions. Such a thermal decyclisation has been realised in the cases of presecamine (138) and villamine (214), both preparatively and in the mass spectrometer. In each case it leads to breakdown of the alkaloid into the monomeric constituents. The reaction of presecamine proceeds so readily that the molecular ion has not been observed.

Further Pyrolysis Reactions. A false molecular weight determination may result from loss of the elements of water, formaldehyde from $HOCH_2–\underset{|}{\overset{|}{C}}–COOMe$ (see ref. 156), acetic acid from acetyl compounds *etc.* In the case of macralstonine (220) the $(M^+ - H_2O):M^+$ ratio is dependent on the structure of the ion source of the mass spectrometer and varies from 100 : 2 to 100 : 62[71,156] (see also ref. 159).

The information to be gained from a mass spectrum is naturally dependent on structure. Serpentinine (253) gives an extremely complicated, worthless spectrum in which no molecular ion appears. The spectrum of *C*-curarine dichloride (54) shows only the molecular ion of the bisnor-base, while for calebassine dichloride (55) only the peaks corresponding to the loss of one and two molecules of water from the bisnor-base are observed. The other curare alkaloids also yield spectra which show a lack of fragment ion peaks; they share this characteristic with strychnine.

The remaining bisindole alkaloids fall into three groups. In the first group only one component fragments in the mass spectrometer. Examples are pycnanthine (193) and relatives. In the second group fragmentation takes place in both components, although only relatively low molecular weight fragment ions are obtained (alkaloids of the voacamine and vinblastine groups, Sections 9 and 10). The most informative mass spectra are those of the 'dimeric' bases in which both components fragment to give rise to fragment ions of both high and relatively low molecular weights. In these cases the fragmentation processes are largely those of the corresponding monomeric alkaloids. To this group belong the *Alstonia* alkaloids (Section 12), vobtusine (255) and related bases, and pleiomutine (230). With the aid of very little other data, the high resolution mass spectrum of pleiomutine (230) allowed the complete structure to be elucidated.

The great importance of D-labelling in the mass spectral examination of bisindole alkaloids has already been indicated in the foregoing sections.

Molecular Weight Determination.—The possible problems encountered in a mass spectrometric molecular weight determination have been dealt with. A decision between monomer and 'dimer', in favourable cases also 'trimer', can

[159] A. Chatterjee and G. Ganguli, *J. Sci. Ind. Res., India*, 1964, **23**, 178.

follow from u.v. spectra (presecamines, Section 8) or pK'_a values if these are different enough.* The method of partial methylation[160] is only applicable to alkaloids in which the two $N_{(b)}$-atoms have similar nucleophilicities. Combustion analyses and standard molecular weight determinations complete the available list of techniques.

Optical Rotatory Dispersion and Circular Dichroism.—The absolute configuration of monomeric indole alkaloids can often be determined from their o.r.d or c.d. curves.[161] In favourable circumstances it is also possible to obtain information concerning the absolute stereochemistry of 'dimeric' indole alkaloids. In order for this to be possible the aromatic Cotton effect of one component must be strong, that of the other component weak. The former will then determine the nature of the Cotton effect of the 'dimer'. The skeleton, and particularly the aromatic chromophore, of the other component must be appreciably further removed from the chromophore determining the Cotton effect than those atoms which determine the sign and amplitude of the Cotton effect in the corresponding monomer. Thus vobtusine (255), which contains methoxyindoline (very weak Cotton effect) and vincadifformine (very strong Cotton effect) components, gives an o.r.d. curve which is extremely similar to that of (−)-vincadifformine (256). The vincadifformine 'half' of vobtusine (255) thus possesses the same absolute stereochemistry as (−)-vincadifformine.[144] The same is true for callichiline (277).[70]

The Origin of Bisindole Alkaloids.—One is forced to ask the question: Are bisindole alkaloids artefacts? The term bisindole alkaloid would generally be applied to such products which can be directly shown to be present in an extract of some part of a plant prepared under mild conditions. The extraction and identification procedures must be such that, on the basis of our chemical knowledge, condensation of monomers which might conceivably be present, and also subsequent secondary reactions of a 'dimer', can be excluded.† The most important indication of a possible artificial genesis is given by the structure of the bisindole alkaloid itself. Unnatural product candidates are those 'dimers' which can be readily synthesised from monomeric precursors under mild conditions: voacamine types (Section 9), the secamines and presecamines (Section 8), geissospermine (105), geissolosimine (125), pleiomutine (230) [and umbellamine (235)?], *C*-toxiferine (38), and above all *C*-dihydrotoxiferine (46). 18-Desoxy-Wieland–Gumlich aldehyde metho-salt (35) dimerises so rapidly to *C*-dihydro-

[160] W. v. Philipsborn, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1956, **39**, 913.

[161] N. Finch, C. W. Gemenden, I. Hsin-Chu-Hsu, A. Kern, G. A. Sim, and W. I. Taylor, *J. Amer. Chem. Soc.*, 1965, **87**, 2229; N. Finch, W. I. Taylor, T. R. Emerson, W. Klyne, and R. J. Swan, *Tetrahedron*, 1966, **22**, 1327; W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron*, 1967, **23**, 365, 375; W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, and H. Schmid, *Helv. Chim. Acta*, 1965, **48**, 443; W. Klyne, R. J. Swan, B. W. Bycroft, and H. Schmid, *ibid.*, 1966, **49**, 832; W. Klyne, R. J. Swan, N. J. Dastoor, A. A. Gorman, and H. Schmid, *ibid.*, 1966, **50**, 115; W. Klyne, R. J. Swan, A. A. Gorman, A. Guggisberg, and H. Schmid, *ibid.*, 1968, **51**, 1168.

* Such methods require confidence in the homogeneity of the product concerned.

† Sophisticated and unambiguous control experiments have to date not been reported. In certain cases extractions under reducing conditions may prove fruitful.

toxiferine (46) that demonstration of the presence of the latter in an extract is no indication of a natural existence. On the other hand, the existence of the main alkaloid *C*-calebassine (55) is an indication of the natural occurrence of *C*-dihydrotoxiferine.

C-Curarine (54) is formed by oxidation of *C*-dihydrotoxiferine (46) under very mild conditions. The alkaloid has, however, repeatedly been isolated from South American *Strychnos* species under conditions which do not suggest that it is an artefact.* The same applies to *C*-alkaloid E (51) formed from *C*-toxiferine (38).

Although presecamine (138), apparently a likely unnatural product candidate, is rapidly formed from the monomer secodine (136), it has been shown that the presecamines are in fact natural products (Section 8). The same is probably true of the secamines, which are formed by rearrangement of the presecamines.

To date, no known bisindole alkaloid has been shown to be only an artefact. In addition, no experimental evidence exists which undermines the assumption that bisindole alkaloids are actually formed from the completed monomeric partners. Support for this idea is derived from the kind of reactions apparently necessary to effect such 'dimerisations' which are known biogenetic processes: amine-aldehyde condensations, Mannich reactions, Michael additions, Friedel–Craft type condensations, Diels–Alder type processes, radical coupling *etc.* The observation that the skeletal distribution amongst monomeric alkaloids is reflected throughout the 'dimeric' series lends further support.

***X*-Ray Analysis.**—The structures of the following bisindole alkaloids or bisindole alkaloid derivatives have been either determined or confirmed by *X*-ray analysis: calycanthine (1) dihydrobromide,[162] chimonanthine (7) dihydrobromide,[163] hodgkinsine (20) trimethiodide,[15] caracurine II dimethiodide (50),[29] *C*-calebassine (55) di-iodide,[30] anhydro-isocalebassine methyl ether di-iodide (64),[32] haplophytine (99) dihydrobromide (absolute configuration),[52] vincristine (170) methiodide (absolute configuration),[102] and villalstonine (213).[122]

18 Pharmacology

Pharmacology of Calabash-curare.†[164,165]—*Paralytic Activity.* A number of *Strychnos* alkaloids have considerably greater paralytic action than any previously known natural or synthetic neuromuscular blocking agent.[166] Unfortunately, frogs are not suitable for the evaluation of curare effects because they show sea-

[162] T. A. Hamor, J. M. Robertson, H. N. Shrivastava, and J. V. Silverton, *Proc. Chem. Soc.*, 1960, 78; T. A. Hamor and J. M. Robertson, *J. Chem. Soc.*, 1962, 194.
[163] I. J. Grant, T. A. Hamor, J. M. Robertson, and G. A. Sim, *Proc. Chem. Soc.*, 1962, 148.
[164] D. Bovet, F. Bovet-Nitti, and G. B. Marini-Bettòlo, eds, 'Curare and Curare-like Agents,' Elsevier Publishing Co., Amsterdam, 1959.
[165] Curare Symposium der Schweiz. Akademie der Medizin. Wissenschaften, Zürich, Schwabe & Co., Vlg. Basel, 1967.
[166] P. G. Waser, *Helv. Physiol. et Pharm. Acta*, Suppl. VIII, 1953, **11**, 1.

* See previous footnote.
† See Section 2.

sonal variation toward many drugs. Therefore, a simple test has been developed. The alkaloid solutions are injected into the tail-veins of mice and the time that elapses before head-drop, abolition of righting reflexes, and death or recovery measured. Compared with the rabbit head-drop method this technique has the great advantage that it requires only small amounts of the rare alkaloids for each experiment, and allows the determination of at least three distinct end-points. Average values are determined for each alkaloid in 20—50 experiments. The combined activities of all the isolated alkaloids equal 99.6 % of the original curare activity of the calabash, indicating the great accuracy of the test method used.

There is a wide variation in the paralytic activity of calabash alkaloids. In Figure 2[167] the limits of the different areas on the abscissa represent the head-drop and the minimal lethal dose for mice; the ordinate indicates the duration of paralysis caused by an intermediate dose (logarithmic scale). Seven alkaloids are found to be more active than *d*-tubocurarine (291); of these *C*-toxiferine (38) is extremely potent. The lethal doses of two alkaloids, *C*-alkaloid G (56) and *C*-alkaloid E (51), are less than 1 μg per kg, indicating that their potency is 100 times greater than that of *d*-tubocurarine (291).

It is surprising that the activities of these two alkaloids, determined by the dose–activity relation for head-drop, diminish appreciably within hours and become constant only after one to two months. These alkaloids seem to change

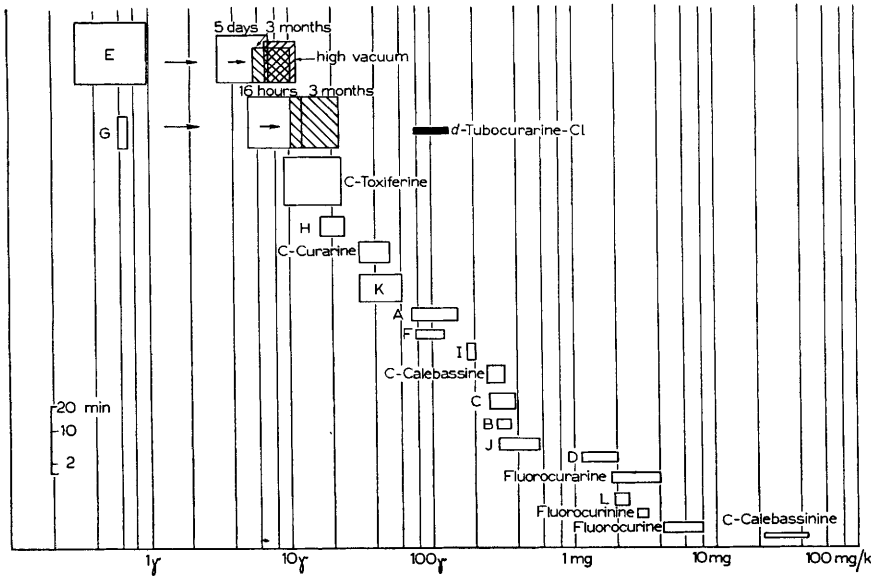
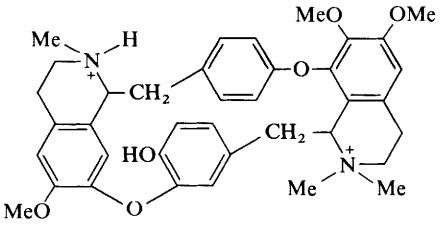
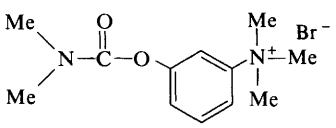


Figure 2[167] *Action in mouse test* (*abscissa*: *dose in* mg *per* kg *mouse*, 1γ = 1 μg; *ordinate*: *duration of paralysis*). *The letters refer to the* C-*alkaloids A*(52), *D*(53), *E*(51), *F*(57), *G*(56), *and H*(49). *Concerning* C-*alkaloids C, I, J, K, and L and* C-*calebassinine*, C-*fluorocurine, and* C-*fluorocurinine see ref. 1.* C-*Fluorocurarine* = (68).

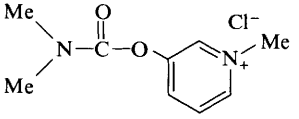
[167] J. Kebrle, H. Schmid, P. G. Waser, and P. Karrer, *Helv. Chim. Acta*, 1953, **36**, 102.



(291), *d*-Tubocurarine



(292), Neostigmine



(293)

their configuration, the stable form having an activity of 10 % or less of the original value. This interesting observation might partly explain the discrepancy between the quick and deadly effect of poisoned arrows and the rather slow and often weak action of isolated alkaloids on laboratory animals and man.

In different chemical groups of calabash alkaloids there are remarkable parallels between curarising potency and polarity, as determined by paper chromatography. The slow-moving alkaloids, which have greater solubility in the water phase, have greater neuromuscular activity than faster moving alkaloids. The differently hydroxylated alkaloids of the three alkaloid triads of *C*-dihydrotoxiferine [namely *C*-dihydrotoxiferine (46), *C*-alkaloid H (49), *C*-toxiferine (38)], *C*-curarine [*C*-curarine (54), *C*-alkaloid G (56), *C*-alkaloid E (51)], and *C*-calebassine [*C*-calebassine (55), *C*-alkaloid F (57), *C*-alkaloid A (52)], show this interesting correlation (Table 5). In all three groups consecutive introduction of hydroxy-functions into the side-chains induces higher curare activity. The most active alkaloids belong to the *C*-curarine triad with an ether oxygen in the central eight-membered ring. The stereochemistry of these molecules seems to be even better suited for maximum curarising action, and must be very similar to that of the *C*-toxiferine group.

The rabbit head-drop test indicates that the alkaloids occurring most abundantly in calabash differ significantly in their paralytic properties: 0.004 mg per kg *C*-toxiferine, 0.025 mg per kg *C*-curarine, and 0.10 mg per kg *C*-calebassine (*d*-tubocurarine: 0.15 mg per kg) cause head-drop of 3 min duration. This effect is antagonised by small doses of neostigmine (292), whereas larger doses prolong the paralytic action.

Figure 3[166] demonstrates the duration of the neuromuscular block produced by some alkaloids after their administration in doses just sufficient to prevent

Table 5 *Pharmacological activities of important curare alkaloids*

Alkaloids	18-CH_2R	18′-CH_2R′	R_c[a]	*Dose (mouse i.v.)* μg per kg		*Duration*[c] *of paralysis* (min)
				Head-drop	*Lowest lethal* LD_{100}[b]	
	R	R′				
C-Dihydrotoxiferine triad						
C-Dihydrotoxiferine (46)	H	H	1.22	30	60	5.5
C-Alkaloid H (49)	OH	H	0.71	16	24	3.7
C-Toxiferine (38)	OH	OH	0.42	9	23	12
C-Curarine triad						
C-Curarine (54)	H	H	1.00	30	50	4
C-Alkaloid G (56)	OH	H	0.65	5	12	7
C-Alkaloid E (51)	OH	OH	0.36	4	8	18
C-Calebassine triad						
C-Calebassine (55)	H	H	0.80	240	320	3
C-Alkaloid F (57)	OH	H	0.49	75	120	1.3
C-Alkaloid A (52)	OH	OH	0.23	70	150	2

[a] Paper chromatogram; the R_c-values are R_f-values standardised relative to *C*-curarine (R_c = 1.00).
[b] LD_{100} is defined as the dose with 100% lethality to all test animals.
[c] At intermediate dose between head-drop dose and LD_{100}.

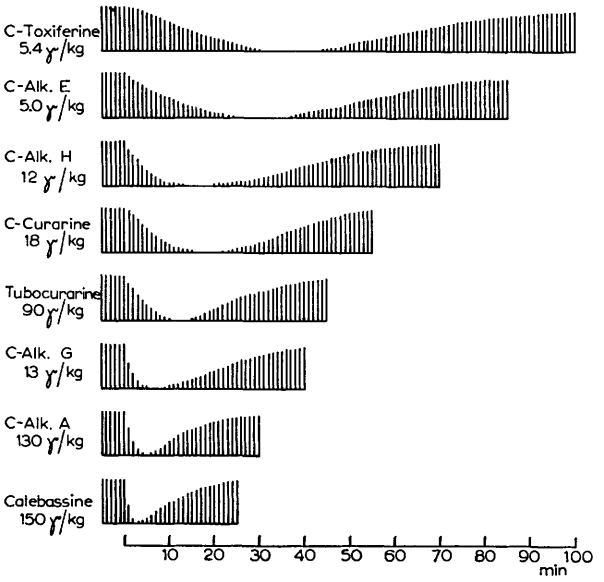


Figure 3 *Duration of paralysis (paralytic dose i.v.), contraction of cat gastrocnemius by electrically stimulated sciatic nerve* (4 × /min).

transmission in the electrically stimulated sciatic-gastrocnemius preparation of cats. Calabash-curare contains various alkaloids with a short action and some with an extremely long action. The duration of action of *C*-toxiferine (38) is outstanding; it takes nearly 2 hours for the muscle to recover after a slow, progressive onset of paralysis. With a 20-fold paralytic dose, total paralysis lasts 8 hours. *C*-Alkaloid E (51) shows similar properties and the action of *C*-curarine (54) is comparable to that of *d*-tubocurarine (291). Respiration may be paralysed before the gastrocnemius muscle. Neostigmine (292) again immediately antagonises all paralytic symptoms. In comparison to intravenous injection, intramuscular injection of *C*-curarine is five times slower and subcutaneous injection ten times slower as regards onset of action. An oral dose of 1.35 mg per kg *C*-curarine paralyses the animal completely within one hour.

With the isolated *rectus abdominis* preparation of frogs the mode of action is found to be of the curare type. Like *d*-tubocurarine, all the alkaloids investigated antagonise acetylcholine contractions. *C*-Alkaloid E (51) and *C*-toxiferine (38) are the most active.[166]

Side-effects on Blood Pressure and Cardiac Activity. Calabash alkaloids with great curarising potency have little effect on blood pressure. With artificial respiration paralytic doses of *C*-toxiferine and *C*-alkaloids H, E, G, and K*

* The structures of *C*-alkaloids B and K are unknown.

have practically no depressing effect (Figure 4).[166] Thirty times the paralytic dose of *C*-toxiferine causes only a slight depression. *C*-Alkaloid E lowers the blood pressure in the case of a 10-fold paralytic dose and *C*-alkaloid H in that of a 4-fold dose.

Like *d*-tubocurarine, alkaloids of the *C*-curarine group usually lower the blood pressure for a short time. The hypotensive effects of the alkaloids of the *C*-calebassine group last somewhat longer. Liberation of histamine may play a rôle in this effect. *C*-Alkaloid B, evidently owing to ganglionic block, lowers the blood pressure before any paralysis occurs.

All curarising substances in high doses will paralyse autonomic synapses. This is the main reason for side-effects, such as lowering of blood pressure, vagus block, changes of the heart rate, and frequency of respiration. Therefore an investigation of ganglionic block in cats, by measuring the contraction of the nictitating membrane after preganglionic (ganglion cervicale superius) stimulation of the sympathetic nerve has been conducted. The ratios of ganglionic and neuromuscular blocking doses are summarised in Table 6.[166]

Blocking of parasympathetic synapses can be demonstrated by the inhibition of the effects of vagal stimulation. The doses required to block parasympathetic transmission are higher than those necessary for sympathetic block. With *C*-

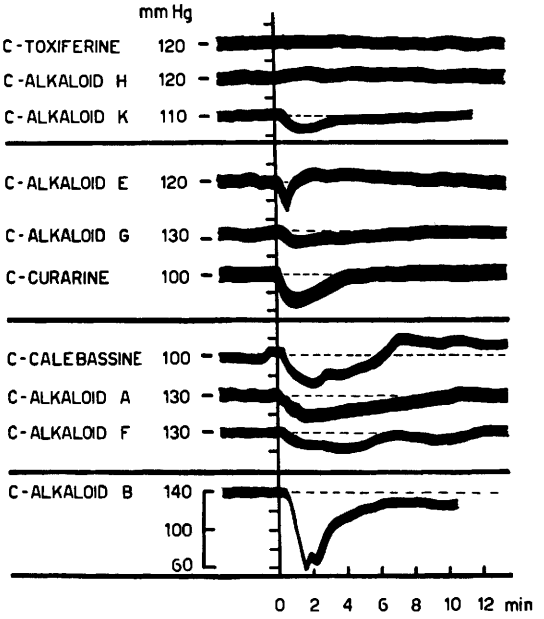


Figure 4 *Blood pressure of cat with artificial respiration after intravenous paralytic doses.*

Table 6 *Ratios of the ganglionic to neuromuscular blocking doses*

Alkaloid	*Partial block*	*Total block*
C-Toxiferine (38)	80	—
C-Alkaloid E (51)	20	24
C-Alkaloid G (56)	20	12
C-Alkaloid H (49)	12	—
C-Curarine (54)	8	8
C-Alkaloid A (52)	5	—
C-Alkaloid K[a]	3	3.5
C-Alkaloid F (57)	3	—
C-Calebassine (55)	2.5	3.3
C-Alkaloid B[a]	0.3	0.8
d-Tubocurarine (291)	11	10
NN'-Diallyl-bisnor-toxiferine (41)	40	50

[a] Structure unknown.

toxiferine in doses of up to 300 μg per kg no changes in vagus effects are detected, but higher doses would probably paralyse the entire autonomic nervous system. Alcuronium [= alloferine, (41)] behaves as favourably as *C*-toxiferine in animal experiments.

Absorption, Distribution, and Elimination. The metabolism of calabash-curare alkaloids has been investigated with ^{14}C-labelled *C*-curarine,[168] ^{14}C-labelled and ^{3}H-labelled *C*-toxiferine, and ^{3}H-labelled *NN'*-diallyl-bisnor-toxiferine.[166,169] Absorption after intramuscular or subcutaneous injection is found to be rapid. In order to achieve the same degree of paralysis as with intravenous injections, approximately ten times as much *C*-curarine is needed if the drug is applied subcutaneously, and 100 times if it is given by stomach tube. In the latter case, paralysis persists until the adminstered drug is completely absorbed. Up to 200 minutes after intravenous injection the largest concentration of alkaloid is found in the liver and the kidneys. The total mass of muscles contains about half as much as the liver and kidney. The blood or muscle curarine concentrations required for paralysis are very small (0.02—0.2 μg per g). The distribution of *C*-curarine in different muscles (gastrocnemius, diaphragm, intercostal muscles) is very similar. The peripheral nerves and the ganglia contain larger amounts of the drug than the spinal cord or the brain. Most of the alkaloids (*C*-toxiferine, *C*-curarine, *C*-alkaloids E, G, and H) are eliminated unchanged by the kidneys (in three hours 25—30% *C*-curarine, in six hours 90% *C*-toxiferine, in four hours

[168] P. G. Waser, H. Schmid, and K. Schmid, *Arch. Internat. Pharmacodyn.*, 1954, **96**, 386.

[169] P. G. Waser and U. Lüthi, *Helv. Physiol. Acta*, 1966, **24**, 259; P. G. Waser and J. Reller, in preparation.

50% alcuronium). A large proportion of these alkaloids is eliminated in the bile (10—15%). Excretion through the intestine is barely detectable.

The short-acting *NN'*-diallyl-bisnor-toxiferine (alcuronium) is accumulated 15—60 minutes after intravenous injection in different tissues in acid mucopolysaccharides (tendons, cartilage, connective tissue *etc.*). This transient binding seems to limit the curare action to a short period of 10—20 min. Metabolism of all investigated alkaloids is small, as only traces of radioactive breakdown products are found in the expired air, but small amounts of other non-labelled metabolites may be formed.

One hundred years ago Claude Bernard[170] demonstrated that curare blocks the neuromuscular junction in frogs. Now, using a special autoradiographic technique, it has been possible to show for the first time an accumulation of labelled curare molecules at their receptor sites in the endplates of mouse diaphragms.[171,172] With densitometric measurements the number of radioactive toxiferine and curarine molecules per endplate can be determined and the kinetics and interactions with cholinergic drug molecules or anticholinesterases investigated.[172] The results are important for the understanding of the molecular action of curarising and depolarising molecules on the post-synaptic membrane.

Clinical Use. Of all investigated calabash alkaloids only *C*-curarine, *C*-toxiferine, and the synthetic *NN'*-diallyl-bisnor-toxiferine (41) have been used clinically.[173] Their advantages compared to other curare compounds are: high selectivity, no depression of blood pressure, no broncho-constriction, no liberation of histamine, the prolonged action of *C*-toxiferine and the short action of (41). A dose of 10—15 mg *C*-curarine paralyses the artificially respirated man of 70 kg for 20—25 min. A second intravenous injection of 5 mg prolongs paralysis to 50—160 min. With these doses no side-effects are observed. Toxiferine is much more potent. Here 2 mg intravenously injected produce paralysis for 50—160 min. Side-effects of circulation or respiration (broncho-constriction) have never been observed. Anticholinesterases such as pyridostigmine (293) (5—10 mg) antagonise the curare action within minutes. Toxiferine is the most active and specific curarising agent for man, and of longest paralytic action. It is therefore especially suited for use in surgical operations of long duration and in the treatment of tetanus.

In contrast to this, alcuronium [= alloferine, (41)] may be used for short operations. Initial intravenous doses of 5—10 mg produce paralysis for 15—20 minutes, and repetitive doses of 2—5 mg may be given. No undesired side-effects have been described and alcuronium is now widely used by anaesthetists.[165]

Pharmacology of *Vinca* Alkaloids.*—*Vinca rosea* plants have enjoyed a popular reputation in indigenous medicine in various parts of the world. They have been

[170] C. Bernard and T. J. Pelouze, *Compt. rend.*, 1850, **31**, 533; 1856, **43**, 825.
[171] P. G. Waser and U. Lüthi, *Arch. Internat. Pharmacodyn.*, 1957, **112**, 272.
[172] P. G. Waser, *Ann. New York Acad. Sci.*, 1967, **144**, 737.
[173] P. G. Waser and P. Harbeck, *Anaethesist*, 1959, **8**, 193 (July); *ibid.*, 1962, **11**, 33 (Febr.).

* See Section 10.

used as analgesic for toothaches, anti-scurvy and haemorrhage treatment, for the proprietary suppression of the flow of the milk, for cleaning and healing chronic wounds, and last but not least, as treatment for diabetic ulcers because of their hypoglycemic activity.[174—179]

In recent years the hypoglycemic activity has been studied by two separate research groups.[178,179 and 96,99,175—177,180—182] Neither group could substantiate any hypoglycemic activity with crude plant extracts,[174] but in the course of the work it was noticed that treated rats frequently suffered a fatal fulminating infection. Investigation showed that the fatal septicemia was secondary to a massive leukopenia.[174,178] It must be considered that any banal infection with one of the ubiquitous germs may cause severe septicemia with subsequent death, when white blood cells, normally dealing with anti-infection mechanisms, are diminished. When white blood cells are diminished, why should malignant cells, which increase their number much faster, not be affected by such treatment? This question stimulated a world-wide search in the field of *Vinca rosea* alkaloids.

First studies were undertaken with Periwinkle plants from Jamaica. The roots, stems, and leaves all contain active material; the leaves contain the highest proportion of activity, but in the seeds almost no activity is found.[178,179] Today we know that four of the pure alkaloids, crystallised from extracts of *Vinca rosea* plants, namely vinblastine [(169), = vincaleukoblastine)], vincristine [(170), = leurocristine], vinleurosine [= leurosine, (183)], and vinrosidine [= leurosidine, (181)] show good effects in suppression of tumour growth. In the last decade about fifty-five alkaloids have been found in *Vinca rosea* extracts and tested for their pharmacological effects.[175,176] Besides the four mentioned none of the others showed significant activity in suppressing cell growth.

Experimentally there are two important ways of detecting anti-tumour activities of *Vinca* alkaloids. One way deals with healthy animals. Products with potencies in cell growth inhibition may first suppress fast growing cells. For this purpose the cells of the circulatory system may serve as subject cells. In healthy mice, rats, guinea pigs, rabbits, or other small animals, the normal blood cell count (red and white cells) is easily established. Any significant drop in the blood cell count after single or repeated doses of substances with possible anti-tumour activities can indicate that these substances are worth further study. The second step involves evaluation of these substances in experimental tumours. One of the most useful models is the P 1534 leukemia in DBA/2 mice, which has

[174] A. Goldstein, L. Aronow, and S. M. Kalman, 'Principles of Drug Action,' Harper Row, New York, 1968, p. 755.
[175] I. S. Johnson, H. F. Wright, and G. H. Svoboda, *J. Lab. Clin. Med.*, 1959, **54**, 830.
[176] I. S. Johnson, J. G. Armstrong, M. Gorman, and J. P. Burnett, *Cancer Res.*, 1963, **23**, 1390.
[177] N. Neuss, M. Gorman, and I. S. Johnson, *Methods in Cancer Research*, 1967, **3**, 633.
[178] R. L. Noble, C. T. Beer, and J. H. Cutts, *Ann. New York Acad. Sci.*, 1958, **76**, 882.
[179] R. L. Noble, *Lloydia*, 1964, **27**, 280.
[180] M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, and N. J. Cone, *J. Pharm. Sci.*, 1959, **48**, 256; G. H. Svoboda, *ibid.*, 1958, **47**, 834.
[181] G. H. Svoboda, M. Gorman, and R. H. Tust, *Lloydia*, 1964, **27**, 203.
[182] G. H. Svoboda, M. Gorman, and M. A. Root, *Lloydia*, 1964, **27**, 361.

played an important rôle in the evaluation of *Vinca rosea* alkaloids.[176,177] Substances which significantly suppress these malignant cells may have a good chance in human cancer therapy. About twenty similar tests for evaluation of anti-tumour activity are listed in ref. 176. After a number of positive therapeutic and toxicological results with small laboratory animals, tests with cats, dogs, and monkeys followed and indicated the usefulness of the *Vinca* alkaloids for human therapy.[176] The only two alkaloids which have passed all these barriers are vinblastine (169) and vincristine (170). They have since undergone extensive clinical studies, which are documented in numerous papers.[176,177,183,184] Both have been found to be useful in the treatment of human cancer.

From the beginning of research with *Vinca rosea* for cancer therapy, numerous scientists have tried to shed light on the mode of action of these alkaloids. Pharmacological studies have shown that these alkaloids rarely pass membranes.[185] This is understandable considering two properties of the *Vinca* molecules. One property concerns their molecular size, the larger the molecules, the less frequently they pass membrane barriers. A second factor which may be even more influential on membrane passage is the polarity. It is well established that polar molecules, at a given pH, do not pass cell membranes. This factor influences absorption from the intestinal tract after oral application. It also prevents penetration to organ systems like the central nervous system (C.N.S.), and affects absorption from the abdominal cavity after intraperitoneal injection. Accordingly, *Vinca* alkaloids, because of their size and particular polarity, have a very low chance of crossing membranes. This has been experimentally established.[185] Given orally they are absorbed only to a small extent. They must be injected, but even then they do not reach everywhere. This is disadvantageous for cancer therapy. Some theoretical considerations may illustrate the clinicians' problems: If one cancer cell survives therapy, it will proliferate to a great number. After 'successful' therapy the tumour may almost disappear; the patient's life may be temporarily saved, but later on the tumour will reappear with the successors of even one surviving cell.[186] Rall has given an apt description of cancer cell behaviour:[185]

> 'The malignant cells of acute leukemia enjoy unusual prerogatives in their battle against successful chemotherapy. Like guerilla forces in jungle warfare, these cells possess hidden sanctuaries into which the attackers cannot penetrate. And in these pharmacological sanctuaries they can, if not completely annihilated, regroup and multiply. One such sanctuary lies within the C.N.S.'

[183] E. Frey, *Lloydia*, 1964, **27**, 364. E. Gmachl: Internationales Symposion über die Anwendung der *Vinca*-Alkaloide Velbe und Vincristin, Urban & Schwarzenberg-Verlag, München, 1969; M. E. Hodes, R. J. Rohn, and W. H. Bond, *Cancer Res.*, 1960, **20**, 1041; W. W. Sutow, M. P. Sullivan, and G. Taylor, *ibid.*, 1965, **25**, 1481; O. H. Warwick, J. M. Darte, and T. C. Brown, *ibid.*, 1960, **20**, 1032.

[184] V. K. Vaitkevicius, R. W. Talley, J. L. Tucker, and M. J. Brennan, *Cancer*, 1962, **15**, 294; V. K. Vaitkevicius, *Vinca*-Alkaloide in der Behandlung des Krebses; in: E. Gmachl: Internationales Symposion über die Anwendung der *Vinca*-Alkaloide Velbe und Vincristin, Urban & Schwarzenberg-Verlag, München, 1969, p. 70.

[185] D. P. Rall, *Cancer Res.*, 1965, **25**, 1572.

[186] H. E. Skipper, *Cancer Res.*, 1965, **25**, 1544.

The human body offers several places where cancer cells may hide. When *Vinca* alkaloids are injected, they cannot reach organs like C.N.S., thymus, testes or even the tumour itself. Because of an inadequate blood supply in the interior of large tumours, the drug cannot reach the centre and this place also may serve as a sanctuary. To overcome this disadvantage experiments of instillation in the C.N.S. have been undertaken with other drugs. *N*-Methyl-aminopterine (Methothrexate) has been applied intrathecally, but even then some places of the C.N.S. remain unaffected.[185] This may explain why reports of successful intrathecal instillation with the relatively toxic *Vinca* alkaloids are still lacking. If local application is possible, good results may be expected for theoretical reasons, and this has been established by clinical tests.[187]

Given intraperitoneally to rats, vinblastine and vincristine reach their maximum concentration in serum after one hour, which then decreases on an exponential scale. Within 24 hours less than 1% of the unchanged substances are found in the urine.[188] This indicates a fast and almost complete metabolism, but 24 hours after a single dose, 20% of the initial cytostatic activity can still be found. This indicates that metabolites have properties similar to the original alkaloids. Tritium-containing metabolites arising from ^{3}H-labelled vinblastine are mainly excreted through the bile, although no such metabolites have been identified.[188,189]

Like colchicine, vinblastine (169) and vincristine (170) develop their potencies during metaphase. They inhibit mitosis *in vitro*[190,191] and *in vivo*.[184,185,191] The cytostatic effect of both alkaloids is often interpreted as an irreversible block of metaphase during cell division. This arrest results from blockage of metabolic mechanisms caused by biochemical reactions which are not well known.[188] Six hours after administration of vinblastine to men who suffered from ascites caused by malignant cells, no post-metaphasic cells could be observed. However, they reappeared 48 hours later. Similar results can be obtained in other tissues with high rates of cell growth.[192] The finding that no post-metaphasic cells can be found has led to the conclusion that cell growth is stopped at this stage.

The action of vinblastine and vincristine on enzyme systems has been studied.[192] Both alkaloids strongly inactivate pH-5-enzymes and DNA-dependent RNA polymerase. In contrast, DNA polymerase and uridine kinase are hardly influenced. Despite successful studies on phenomena of *Vinca* alkaloid

[187] K. Brandl, Lokale und parenterale zytostatische Therapie weiblicher Genitalkarzinome mit Vinblastin; in: E. Gmachl: Internationales Symposion über die Anwendung der *Vinca*-Alkaloide Velbe und Vincristin, Urban & Schwarzenberg-Verlag, München, 1969, p. 124.

[188] N. E. Fusenig and P. Obrecht, Der Wirkungsmechanismus der *Vinca*-Alkaloide; in: E. Gmachl: Internationales Symposium über die Anwendung der *Vinca*-Alkaloide Velbe und Vincristin, Urban & Schwarzenberg-Verlag, München, 1969, p. 141.

[189] C. T. Beer and J. F. Richards, *Lloydia*, 1964, **27**, 352.

[190] H. Lettré, Zellstudien mit *Vinca* Alkaloiden *in vivo* und *in vitro*; in: E. Gmachl: Internationales Symposion über die Anwendung der *Vinca*-Alkaloide Velbe und Vincristin, Urban & Schwarzenberg-Verlag, München, 1969, p. 137.

[191] C. G. Palmer, D. Livengood, A. Warren, P. J. Simpson, and I. S. Johnson, *Exptl. Cell Res.*, 1960, **20**, 198.

[192] P. Warnecke and S. Seeber, *Z. Krebsforsch.*, 1969, **73**, 67.

actions,[176,189,193] the chemical reaction mechanisms (where the alkaloids may act with known receptors and so influence malignant cell growth) still remain to be discovered.

Despite only a minor difference in the chemical structures of vinblastine and vincristine, the clinical effects differ considerably. Surprisingly there is no clinical evidence of cross resistance between them, or with radiation and other presently known oncolytic agents.[176] The rise and fall of the blood activity level of vincristine is steeper than that of vinblastine.[188] The dosage requirements of both alkaloids differ markedly: the weekly intravenous dose of vinblastine for humans is 0.1—0.2 mg per kg, that of vincristine, however, is approximately one tenth of this. Concerning the side-effects, vincristine shows more neurotoxic effects and vinblastine is considered to have more potency in bone-marrow depression. This is not without consequences on human therapy: therapy is limited by bone-marrow depression with vinblastine and neuromuscular effects with vincristine. Early symptoms of side-effects are vomiting, fever, and exanthemes. Late symptoms are C.N.S. disturbances, alopecia, and leukopenia. C.N.S. disturbances are manifested by various symptoms such as paresthesias, neuritis, paresis, and muscular atrophy, accompanied by quenched reflexes. Even behaviour may be affected after a long period of treatment.[194] But why do all these side-effects happen, when *Vinca* alkaloids are unable to pass the blood–brain barrier? The only explanation we have at hand is that they are possibly caused by metabolites or breakdown products of the normal biochemical pathways, which are disturbed by the alkaloids.

As mentioned earlier, the *Vinca* alkaloids also suppress normal cells when they are dividing. Severe erythroid hypoplasia of the bone marrow develops in rabbits within 48 hours, when a single dose of 0.1 mg per kg is given intravenously. Subsequent bone marrow samples reveal rapid regeneration until a hyperplastic state is reached after six days. Repeated injection of 0.1 mg per kg every six days over a period of five weeks resulted in a cyclic hypoplastic and hyperplastic state in the erythroid elements. The cycle of hypoplasia followed by rebound hyperplasia was similar to that produced by a single injection. The predominant morphological effect with erythroid depression was the same as in malignant cells: metaphase arrest. The serum iron levels and per cent saturation of iron-binding proteins in the blood reflect these changes of erythropoietic underproduction and subsequent overproduction.[195]

In order to decrease the severe side-effects such as the aforementioned suppression of normal cell growth (normal red and white blood cells are diminished to a number below their physiological threshold), various modifications of the pure plant alkaloid molecules have been tested. One of these modifications,

[193] J. F. Richards and C. T. Beer, *Lloydia*, 1964, **27**, 346.

[194] E. Eckler, Nebenwirkung der Vincristin-Behandlung; in: E. Gmachl: Internationales Symposion über die Anwendung der *Vinca*-Alkaloide Velbe und Vincristrin, Urban & Schwarzenberg-Verlag, München, 1969, p. 214; K. Kendel, H. J. Freund, and P. Obrecht, Neurologische und elektromyographische Studien über Vincristin Effekte, *ibid.*, p. 218.

[195] M. E. Nesbit and J. T. Lowman, *Blood*, 1969, **34**, 633.

vinglycinate sulphate, has been tested clinically. It shows some advantages over the natural products, but generally is not superior to them.[196] Contrary to vinblastine and vincristine, which both cause more or less severe leukopenia, leurosine produces leukocytosis in non-leukemic patients. However, despite its suppressive effect on the experimental P-1534 leukemia, leurosine only negligibly influences human cancers.

Other alkaloids from *Vinca rosea* show a different property: vincolidine, lochrovicine, catharanthine (172), and vindolidine have been shown to possess diuretic activity.[197] Vindolidine has been found to be a potent diuretic,[181] but because of the availability of other harmless diuretics, these alkaloids have not been used for this purpose.

Finally, the reputation of folkloristic medicine has been rehabilitated: it has been shown that the pure alkaloids catharanthine (172), leurosine (183), lochnerine, tetrahydroalstonine, vindoline (171), and vindolinine show some activity in lowering blood sugar.[182] This fact has been established in fasted rats.[182] In the case of skin cancers the magicians really might have cleaned and healed 'chronic wounds'.

In conclusion, we wish to express our gratitude to the many alkaloid chemists and colleagues who have readily provided preprints and unpublished information, and to Frau R. Waldvogel and Miss L. Shandley for their excellent typing.

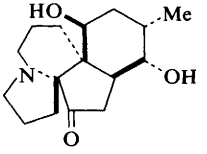
[196] J. G. Armstrong, R. W. Dyke, P. J. Fouts, J. J. Hawthorne, C. J. Jansen, and A. M. Peabody, *Cancer Res.*, 1967, **27**, 221.
[197] M. Gorman, R. H. Tust, G. H. Svoboda, and K. Le Men, *Lloydia*, 1964, **27**, 214.

15
Lycopodium Alkaloids

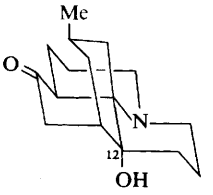
BY V. A. SNIECKUS

A comprehensive review on this topic is available[1] and another is scheduled to appear shortly.[2]

Two common alkaloids have been isolated from *Lycopodium volubile*,[3] and a new one has been readily transformed into a known base.[4] The configuration at C-4 in the novel alkaloid serratinine has been reassigned as in (1) on the basis of an *X*-ray crystallographic analysis.[5] The previous tentative assignment was based on consideration of the mechanism of a Hofmann elimination reaction. Since the other two alkaloids exhibiting this skeleton have been correlated[6] with serratinine, their configurational assignments must be revised accordingly. The structure (2) has been assigned[7] to L. 23, an alkaloid which was originally isolated by Manske and Marion 24 years ago. Chemical correlation of (2) with lycodoline, a base epimeric at C-12 and at N, has been achieved. The alkaloid L. 23 (2) showed an interesting σ-coupled *p*-interaction of nitrogen with the carbonyl function as determined by c.d. measurements. The structural elucidation of



(1)



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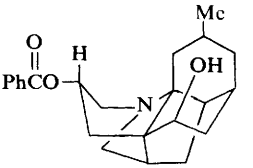


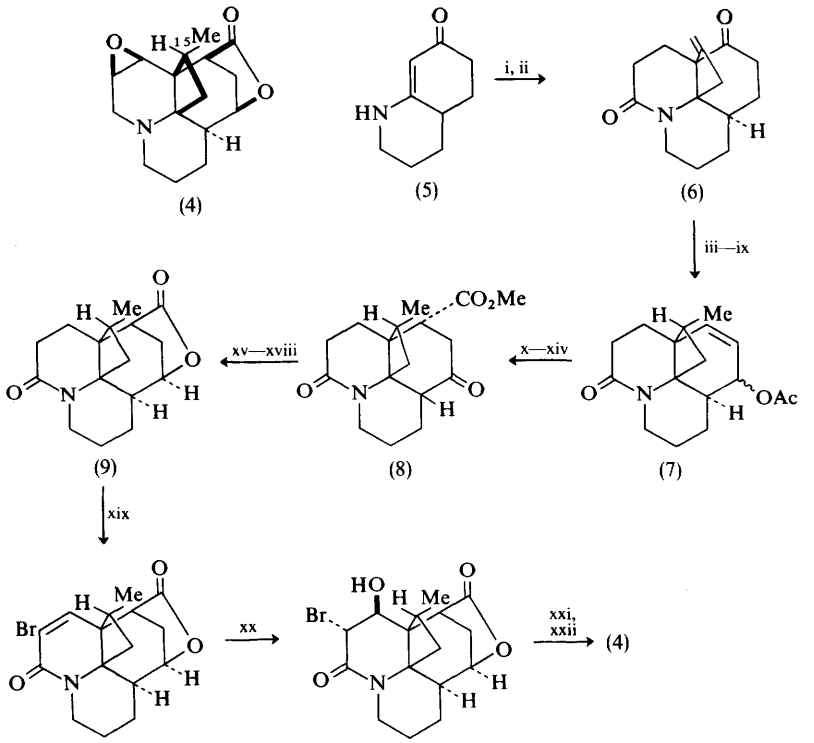
(3)

[1] D. B. MacLean in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1968, Vol. X, p. 305.
[2] W. A. Ayer in 'Organic Substances of Natural Origin,' eds. W. I. Taylor and A. R. Battersby, Marcel Dekker, Inc., New York; personal communication from Professor Ayer.
[3] S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 1317.
[4] W. A. Ayer and B. Altenkirk, *Canad. J. Chem.*, 1969, **47**, 499.
[5] K. Nishio, T. Fujiwara, K. Tomita, H. Ishii, Y. Inubushi, and T. Harayama, *Tetrahedron Letters*, 1969, 861.
[6] Y. Inubushi, T. Harayama, M. Akatsu, H. Ishii, and Y. Nakahara, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 2463.
[7] W. A. Ayer, B. Altenkirk, R. H. Burnell, and M. Moinas, *Canad. J. Chem.*, 1969, **47**. 449.

alopecurine (3), a new type of *Lycopodium* alkaloid, has been accomplished mainly by resorting to *X*-ray crystallographic analysis.[8] Another alkaloid, alolycopine, has been shown to have a serratinine-type structure by direct correlation.[9]

Evidence for the stereochemistry of C-15 in annotinine (4) has been obtained for the first time from a chemical degradation.[10]

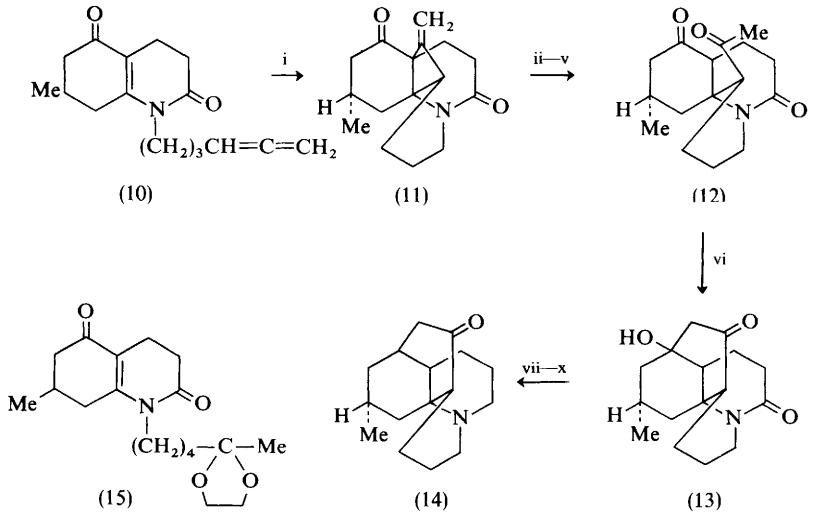
Despite the fact that two syntheses of lycopodine have been reported,[11] synthetic activity in this area has not diminished. A total synthesis of optically active annotinine (4) has been achieved.[12] The readily available vinylogous lactam



Reagents: i, $CH_2{=}CHCO_2H$; ii, $CH_2{=}C{=}CH_2$, *hν*; iii, $(CH_2OH)_2$, TsOH; iv, Pt, H_2; v, H_3O^+; vi, $NaBH_4$; vii, $MeSO_2Cl$, pyridine; viii, Bu^{t}OK, Me_2SO; ix, SeO_2, HOAc; x, OH^-; xi, CrO_3, pyridine; xii, HCN, DMF; xiii, H_2SO_4, MeOH, then hydrolysis (MeOH–KOH), and resolution (brucine); xiv, CH_2N_2; xv, Ac_2O, TsOH; xvi, $NaBH_4$, MeOH–THF; xvii, H_3O^+; xviii, TsOH; xix, NBS, *hν*; xx, aq. HBr; xxi, $NaHCO_3$; xxii, PtO_2, MeOH, HCl.

[8] W. A. Ayer, B. Altenkirk, N. Masaki, and S. Valverde-Lopez, *Canad. J. Chem.*, 1969, **47**, 2449.
[9] W. A. Ayer and B. Altenkirk, *Canad. J. Chem.*, 1969, **47**, 2457.
[10] Tse-Lok Ho, *Tetrahedron Letters*, 1969, 1307.
[11] J. A. Joule, *Ann. Reports*, 1968, **65***B*, 504.
[12] K. Wiesner, L. Poon, I. Jirkovsky, and L. Fishman, *Canad. J. Chem.*, 1969, **47**, 433.

(5) was converted in two steps into the advanced intermediate (6). The orientation of the exciting photochemical reaction was predicted but nevertheless was fully established by degradation. Several unequivocal steps produced the allylic acetate (7) which was eventually transformed into the keto-ester (8). Resolution of the carboxylic acid corresponding to (8) was effected *via* its brucine salt and further steps were carried out on optically active material. The enol acetate of (8) was reduced to a mixture of epimeric alcohols, part of which yielded the lactone (9). The remaining steps are unexceptional excluding the ultimate reaction, which yields annotinine (4) by an unusual hydrogenolysis reaction.

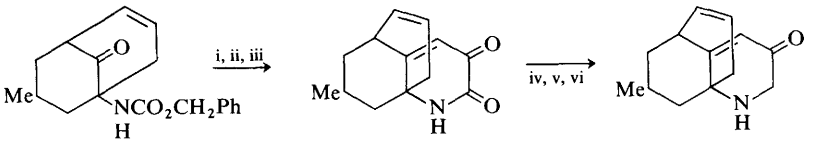


Reagents: i, $h\nu$,THF; ii, $(CH_2OH)_2$, H^+; iii, $PhCO_3H$; iv, $LiBH_4$; v, 1% HCl; vi, NaOH; vii, PCl_5, CH_2Cl_2; viii, Zn, HOAc; ix, $LiAlH_4$; x, H_2CrO_4, H_2SO_4.

An intramolecular counterpart of the photochemical step used in the formation of (6) has been successfully applied to the synthesis of 12-epi-lycopodine (14).[13] Photolysis of (10) yielded the intermediate (11) which was converted into the diketone (12). The latter compound gave the aldol product (13) which, in four steps, produced 12-epi-lycopodine (14). An amazing simplification of the overall route resulted when it was found that the diketolactam corresponding to the ketal (15) underwent a stereospecific Michael reaction to give (13) directly in 30% yield.

A totally different synthetic approach towards lycopodine *via* bicyclo[3,3,1]-nonane intermediates has been partially completed.[14] Curtius rearrangement of the appropriate acyl azide yielded the bridgehead urethane (16) which was

[13] K. Wiesner, V. Musil, and K. J. Wiesner, *Tetrahedron Letters*, 1968, 5643.
[14] Z.-I. Horii, S.-W. Kim, T. Imanishi, and I. Ninomiya, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 2107.



(16) (17) (18)

Reagents: i, HBr, HOAc; ii, $POCl_3$, $MeCOCO_2H$, Et_3N; iii, NaH, THF; iv, $Et_3O^+BF_4^-$; v, $LiAlH_4$; vi, H_2CrO_4, H_2SO_4.

converted into the tricyclic compound (17). Reduction of (17) was facilitated by initial formation of an iminoether. An allylic alcohol was obtained which was oxidised to (18).

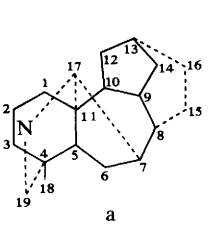
16
Diterpenoid Alkaloids*

BY O. E. EDWARDS

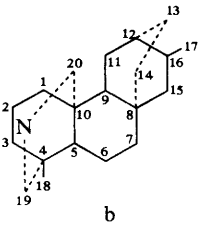
1 Introduction

The emphasis in work related to diterpenoid alkaloids has shifted from structure determination to partial and total synthesis. *X*-Ray crystallography played the major rôle in the structure work and in interpretation of unusual chemistry. However, some interesting new chemical and spectroscopic observations, and analyses of mass spectra, have been reported.

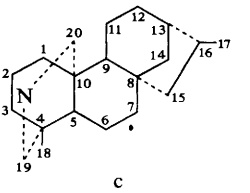
The numbering system for the alkaloids with basic lycoctonine (a), atisine (b), or veatchine (c) skeletons used in this review is in accord with proposals initiated by Dr. J. W. Rowe and approved by Professors S. W. Pelletier, K. Wiesner, and the author. The numbering of these will be carried into that of their more highly bridged relatives.



a



b



c

A comprehensive review, covering the literature up to early 1968, has been provided by Pelletier and Keith.[1] A somewhat abridged version by the same authors has also appeared.[2] The reviews by Fujita and Fujita[3] on the chemistry

[1] S. W. Pelletier and L. H. Keith in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1970, Vol. 12, pp. 1—206.

[2] Chemistry of the Alkaloids, ed. S. W. Pelletier, D. van Nostrand Reinhold, New York, 1970, Chapters 17 and 18.

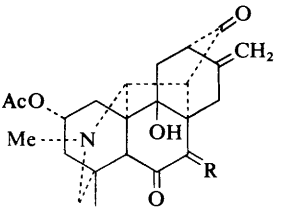
[3] E. Fujita and T. Fujita, *Bull. Inst. Chem. Res. Kyoto Univ.*, 1969, **47**, 522 and preceding reviews.

* Taxane and its derivatives have not been included in this chapter, since none of the *Taxus* constituents recently isolated contains nitrogen. These are properly regarded as diterpene derivatives, and are reviewed as such by Dr. J. Hanson in the Specialist Periodical Report on Terpenes and Steroids (Senior Reporter: Dr. K. Overton).—J.E.S.

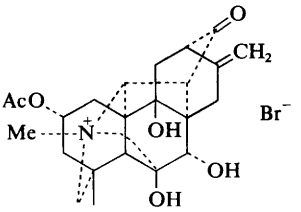
of diterpenoids are valuable but are about a year and a half delayed. The present review deals mainly with the literature from January 1, 1969 to July 1, 1970.

2 *Aconitum*, *Delphinium*, and *Spiraea* Alkaloids

A. New Structures.—*Miyaconitine* ($C_{23}H_{29}NO_6$) *and Miyaconitinone* ($C_{23}H_{27}NO_6$). These alkaloids from *Aconitum miyabei* appeared from their empirical formulae and functionality to be hexacyclic tertiary bases, related as α-ketol and α-diketone (λ_{max} 423 nm, log ε 1.6) respectively.[4] Structures (1) and (2) were proposed for these on chemical and spectroscopic grounds. This was confirmed, and relative and absolute stereochemistry provided, by an *X*-ray crystallographic analysis of miyaconitine hydrobromide[5] [see (3)].



(1), R = —H, ···OH
(2), R = O



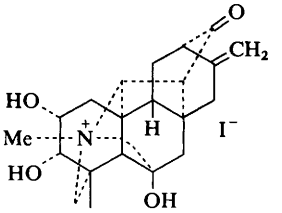
(3)

The α-ketol carbonyl of miyaconitine has a remarkably low i.r. frequency (ν_{max} 1678). This must be due in part to hydrogen bonding and in part to partial single bond character because of $\geqslant N\cdots C{=}O$ interaction. Indeed, the carbonyl absorption was absent in salts of the base, with full development of the transannular bond. The authors used this to locate the ketol system in ring A or ring B. This interpretation was confirmed by the *X*-ray analysis.

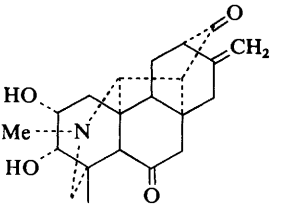
The remaining structural inference depended considerably on interpretation of spectroscopic anomalies. These will be discussed later. The location of the carbonyl on the bicyclo[2,2,2]octane system is of biosynthetic interest (see Section 2E).

Hetidine ($C_{21}H_{27}NO_4$). An *X*-ray analysis[6] of the hydriodide of this minor base from *A. heterophyllum* showed it to have structure (4), from which it follows that hetidine is (5) (absolute stereochemistry assumed). Its anomalous u.v. spectrum (λ_{max} 209 nm, ε 5200) and its biosynthetic interest will be discussed later.

[4] Y. Ichinohe, M. Yamaguchi, N. Katsui, and S. Katimoto, *Tetrahedron Letters*, 1970, 2323.
[5] H. Shimanouchi, Y. Sasada, and T. Takeda, *Tetrahedron Letters*, 1970, 2327.
[6] S. W. Pelletier, K. N. Iyer, V. K. Bhalla, M. G. Newton, and R. Aneja, *Chem. Comm.*, 1970, 393.

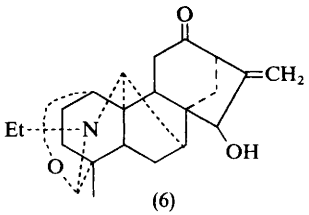


(4)



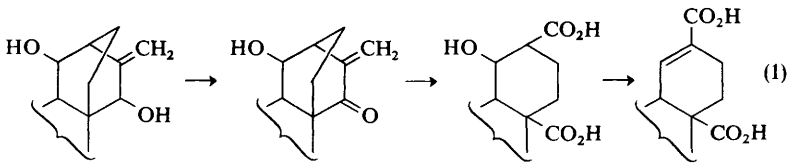
(5)

Songoramine ($C_{22}H_{29}NO_3$). This new base[7] from *A. karakolicum* and *A. songoricum* analysed for a dehydrosongorine. Spectra showed the presence of an *N*-ethyl group, an exocyclic methylene group, and a carbonyl group in a probable β–γ relation to the latter (ν_{max} 1722 cm^{-1} shifting to 1690 cm^{-1} when the double bond was reduced; λ_{max} 295 nm, log ε 2.60) (see section 2B). The presence of a carbinolamine ether was shown by reductive opening and immonium salt formation (ν_{max} 1665 cm^{-1}). The fully reduced alkaloid was identical with dihydrosongorine. Finally, oxidation of songorine with silver oxide gave songoramine. Since the structure of songorine is certain (ref. 1, pp. 137—142), songoramine is (6). The mass spectra of songoramine, songorine, and dihydrosongorine and its diacetate were analysed. These are discussed in Section 2D.



(6)

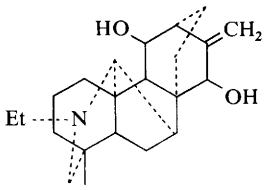
Denudatine ($C_{21}H_{33}NO_2$). *Delphinium denudatum* was the source of this alkaloid.[8] The presence of an atisine-type skeleton was inferred from the presence of an allyl alcohol system which rearranged in the presence of palladium on charcoal to a methyl ketone with ν_{max} 1710 cm^{-1}. The location of a hydroxy-group on the bicyclo[2,2,2]octane system followed from the reactions in equation (1), performed on the derived lactam. The unsaturated acid had λ_{max} 216 nm, log ε 4.29.



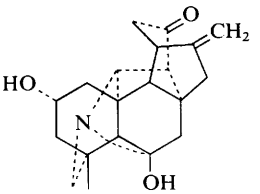
(1)

[7] M. S. Yunusov, Ya. V. Rashkes, S. Yu. Yunusov, and A. S. Samatov, *Khim. prirod. Soedinenii*, 1970, 101.
[8] M. Götz and K. Wiesner, *Tetrahedron Letters*, 1969, 4369.

An *X*-ray analysis[9] confirmed this assignment and proved the structure and stereochemistry to be that illustrated in (7). The structure was also deduced by *X*-ray analysis of denudatine methiodide.[10] The biosynthetic implications of this structure are discussed in Section 2E.



(7)

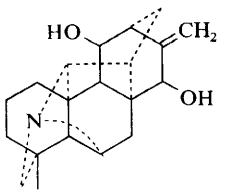


(8)

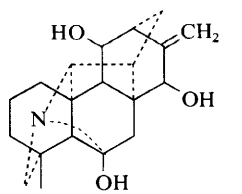
Delnudine ($C_{20}H_{25}NO_3$). This unusual new alkaloid was found in *D. denudatum*.[11] Its empirical formula ($C_{20}H_{25}NO_3$) coupled with the presence of a carbonyl and exocyclic methylene group (δ 4.72, 4.96) indicated a heptacyclic structure. The proximity of the ketone and double bond was concluded from the u.v. absorption (λ_{max} 300 nm, log ε 1.76) (see Section 2B). The presence of a carbinolamine was shown by formation of an *N*-acetyl ketone on acetylation, and that of a secondary hydroxyl near the nitrogen by the pK_a drop of two units when it was oxidised to a carbonyl group.

Structure (8), which was consistent with this evidence, was determined by *X*-ray analysis of delnudine hydrochloride.[12] For biosynthetic speculation see Section 2E.

Kobusine ($C_{20}H_{27}NO_2$) and *Pseudokobusine* ($C_{20}H_{27}NO_3$). The structure of kobusine seemed reasonably secure on chemical and spectroscopic grounds. However, the configuration of the hydroxy-groups on the bicyclo[2,2,2]octane system was uncertain. An *X*-ray analysis[13] of kobusine methiodide has now shown it to have structure (9). It follows that pseudokobusine has structure (10) (ref. 1, pp. 182—185).



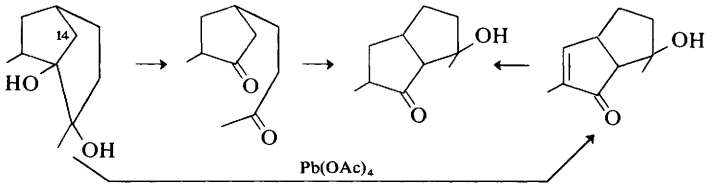
(9)



(10)

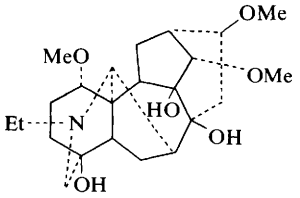
[9] F. Brisse, *Tetrahedron Letters*, 1969, 4373.
[10] L. H. Wright, M. G. Newton, S. W. Pelletier, and N. Singh, *Chem. Comm.*, 1970, 359.
[11] M. Götz and K. Wiesner, *Tetrahedron Letters*, 1969, 5335.
[12] K. B. Birnbaum, *Tetrahedron Letters*, 1969, 5245.
[13] S. W. Pelletier, L. H. Wright, M. G. Newton, and H. Wright, *Chem. Comm.*, 1970, 98.

Lappaconitine ($C_{32}H_{44}N_2O_8$). This is the *N*-acetylanthranilic ester of a trihydroxy-trimethoxy base, lappaconine ($C_{23}H_{37}O_6N$). A recent chemical study[14] located some of its functions on a presumed lycoctonine skeleton. The sequence in equation (2) uniquely located the vicinal glycol group if this skeleton were correct. A methoxy-group was placed on C-14 because of its exceptional ease of hydrolysis (presumably in the diketone). However, β-methoxy elimination



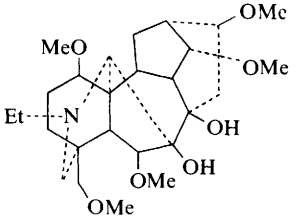
(2)

followed by hydration could account for this observation. An *X*-ray analysis of lappaconine hydrobromide gave a structure (11) containing these features.[15] The absence of C-18 and the 6-methoxy-group, and the oxygen on C-9 are so far unique for the lycoctonine or aconitine groups of alkaloids. See Section 2E for biosynthetic comment.

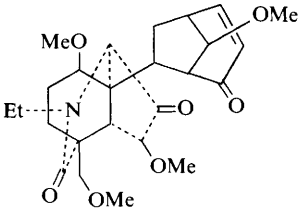


(11)

Delphatine ($C_{26}H_{43}NO_7$). This alkaloid from *D. biternatum*[16] was assigned structure (12) (18-*O*-methyl-lycoctonine). Oxidation to a lactam by permanganate, cleavage by periodate, and treatment with acid gave a desmethanolseco-diketone (13). Hydrogenation of this over platinum followed by methylation

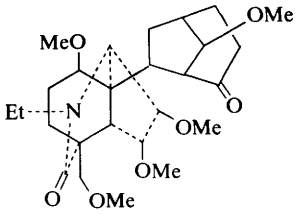


(12)



(13)

[14] N. Mollov, M. Tada, and L. Marion, *Tetrahedron Letters*, 1969, 2189.
[15] G. Birnbaum, *Tetrahedron Letters*, 1969, 2193.
[16] M. S. Yunosov and S. Yunosov, *Doklady Akad. Nauk S.S.S.R.*, 1969, **188**, 1077.

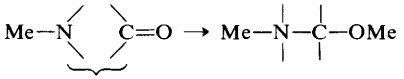


(14)

gave a product (14) which was identical with a compound produced in the same way from lycoctonine.

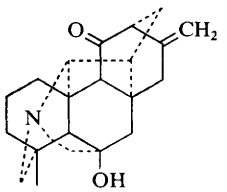
Mesaconitine Isomer. An alkaloid of *A. sachilinense*[17] had the extended formula $C_{19}H_{19}(OMe)_4(OH)_3(OCOMe)(OCOC_6H_4OMe(p)(NMe)$ and hence was isomeric with mesaconitine. It gave the characteristic pyro reaction, so belonged in the aconitine family. On hydrolysis it gave an isomer of mesaconitine.

Spiradines A, B, and C. Although some of the functions were defined by chemical and spectroscopic means, the structure (15) of spiradine A from *Spiraea japonica* L. fil. was determined by *X*-ray analysis of its methiodide.[18] It is thus a close relative of hetisine. The interesting chemical features were its pK_a (see Section 2B), its acetylation to an *N*-acetyl ketone and a basic *O*-acetate, and its reaction with methyl iodide. The first stage in attempted Hofmann degradation (equation 3) gave the *N*-methyl ketone. Further methylation and treatment with silver

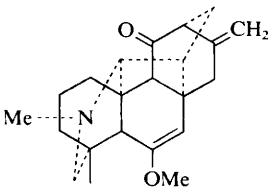


(3)

oxide gave the enol ether (16). Spiradine B and C had the same skeleton but a hydroxy-group and an acetoxy-group at C-11, respectively.



(15)

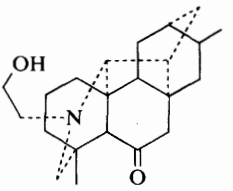


(16)

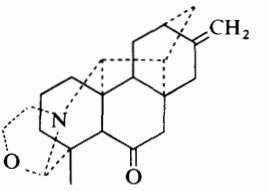
Spiradine D. This alkaloid from *S. japonica* was shown[19] to contain a carbonyl group, an exocyclic methylene group, and an ether group. Sodium borohydride

[17] Y. Ichinoka and M. Yamaguchi, *Bull. Chem. Soc. Japan*, 1969, **42**, 3038.
[18] G. Goto, K. Sasaki, N. Sakabe, and Y. Hirata, *Tetrahedron Letters*, 1968, 1369.
[19] G. Goto and Y. Hirata, *Tetrahedron Letters*, 1968, 2989.

reduced it to a dihydrohydroxy base without loss of oxygen. This, the two extra carbons relative to spiradine A, and a one-hydrogen singlet at δ 4.22 (N–CH–O) suggested the presence of an oxazolidine ring as in atisine. The carbonyl group was in ring A or B if the alkaloid was diterpenoid (pK_a of 9.35, and the formation of a quaternary rather than an immonium salt). In view of the general resemblance to spiradine A an interrelation was attempted. The 11-carbonyl of (15) was removed by Wolff–Kishner reduction, the nitrogen alkylated using β-chloroethanol, and the double bond reduced. The product (17) was also prepared by borohydride reduction of spiradine D, followed by hydrogenation. Thus spiradine D has structure (18). The inertness of the 6-ketone to reduction is surprising.

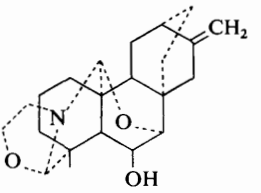


(17)

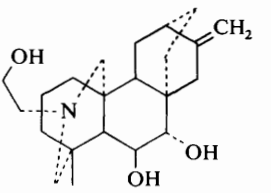


(18)

Spiradines F and G. Spiradine G has been assigned structure (19) by Toda and Hirata.[20] Spiradine F is its monoacetate. The empirical formula fitted an atisine derivative. The presence of an exocyclic methylene group on a six-membered ring (permanganate cleavage to a cyclohexanone) fitted this. The presence of two carbinolamine ether groups was shown by borohydride reduction to a tetrahydro-triol (20). Catalytic reduction produced a saturated triol, which on selenium



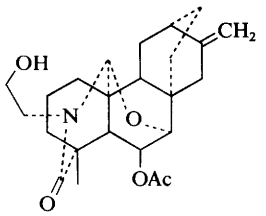
(19)



(20)

dehydrogenation gave 6-isopropyl-1-methylphenanthrene. This too corresponds to the presence of an atisine skeleton. That one ether was an oxazolidine was evident from two coupled triplets at δ 2.47 and 3.59 in (20). Its location in the isoatisine position followed from oxidation of spiradine G to a hydroxy-lactam (21). The location of the other ether bridge was shown when (19) was transformed into a ketone (22), and then into an enolised α-diketone (23). This function must be in ring B, hence (19) is a plausible structure for spiradine G. The β-configuration

[20] M. Toda and Y. Hirata, *Tetrahedron Letters*, 1968, 5565.



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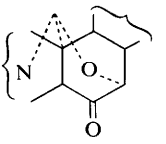
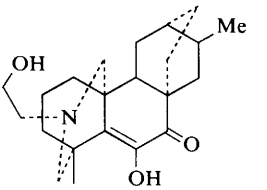


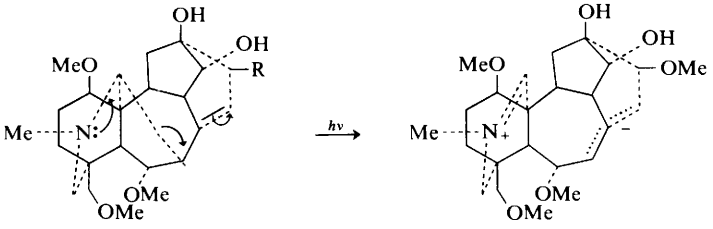
(22)



(23)

of the 6-hydroxy-group was assigned from the effect of acetylation on the n.m.r. signal for the *C*-methyl group (downfield shift of 0.27 p.p.m.). The absolute stereochemistry followed from its M_D of $-479°$ (compared with that of ajaconine) and the o.r.d. curve of ketone (22) (molecular amplitude $+4700°$ compared with $-7300°$ for 5α-cholest-6-one).

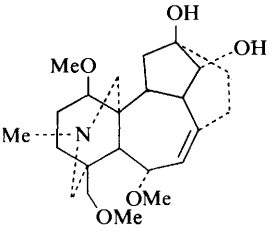
B. Chemistry and Physical Properties.—*The 'Pyro' Chromophore.* The apparent diene chromophore in the 'pyro' compounds derived from the aconitine family of alkaloids was first observed[21] in 1952. It was not until 1960, when the structure of the pyro-compounds was secure, that an explanation for this was proposed.[22] For the case of pyrodelphonine the proposed excitation is illustrated in (24; R = OMe) → (25). Since then, other examples of this type of chromophore have



(24) (25)

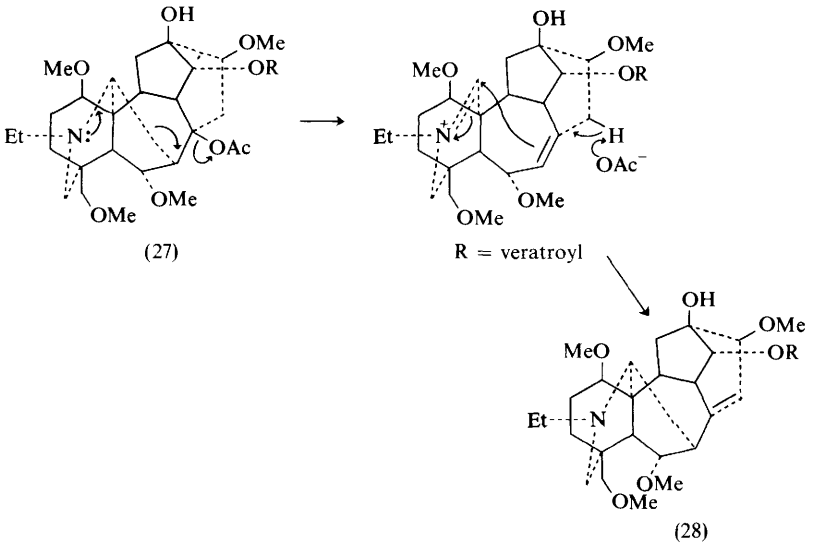
been described.[23] Recently, photolysis of 16-desmethoxypyrodelphonine (24; R = H) in methanol in the presence of sodium borohydride has apparently trapped the photoexcited state by reduction of the immonium ion,[24] giving the 7,17-seco-olefin (26). Use of sodium borodeuteride gave (26) containing one deuterium atom. Hence the general conception of the nature of this unusual chromophore seems correct.

[21] O. E. Edwards and L. Marion, *Canad. J. Chem.*, 1952, **30**, 627.
[22] K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Babin, F. Bickelhaupt, J. Kallos, and T. Bogri, *Tetrahedron Letters*, 1960, No. 3, 17.
[23] R. C. Cookson, J. Henstock, and J. Hudec, *J. Amer. Chem. Soc.*, 1966, **88**, 1060.
[24] K. Wiesner and T. Inaba, *J. Amer. Chem. Soc.*, 1969, **91**, 1036.



(26)

7,17 and 8,17 Bond Fission. A group of interesting reactions of the alkaloids with a lycoctonine skeleton involve rupture of the 7,17 bond. These include the reduction described above and the 'pyro' derivative formation as in the transformation of bikhaconitine (27) into pyrobikhaconitine (28). The ionic intermediate was trapped by hydride reduction.[25] Other early examples of the lability of this bond are the Hofmann degradation of delphonine methiodide[26] (29) → (30), the pyrolysis[27] of aconitine *N*-oxide (31) to give (32), and the formation[28] of hydroxylycoctonine (34) from lycoctonine (33).



(27)

R = veratroyl

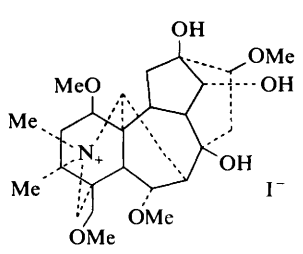
(28)

[25] O. E. Edwards, *Chem. Comm.*, 1965, 318.

[26] K. Wiesner, F. Bickelhaupt, D. R. Babin, and M. Götz, *Tetrahedron Letters*, 1959, No. 3, 11.

[27] K. Wiesner, M. Götz, O. C. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown, and G. Büchi, *Tetrahedron Letters*, 1959, No. 2, 15.

[28] [a] Z. Valenta and T. G. Wright, *Tetrahedron*, 1960, **9**, 284; [b] O. E. Edwards, M. Los, and L. Marion, *Canad. J. Chem.*, 1959, **37**, 1996.



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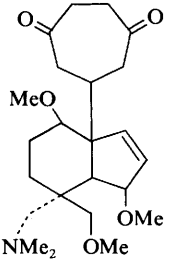

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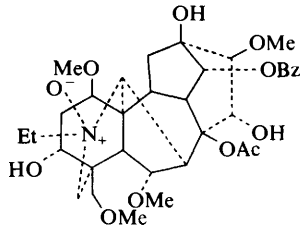
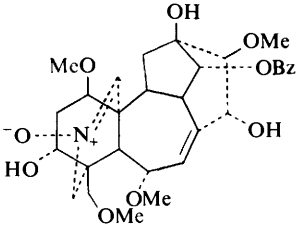


(31)



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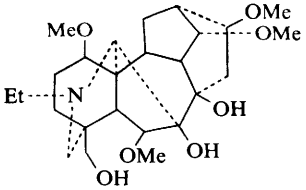
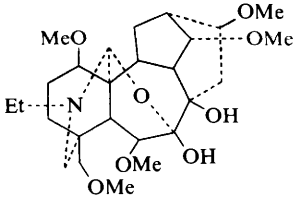


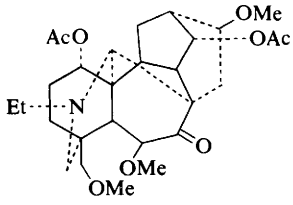
(33)

Pb(OAc)$_4$



(34)

An analogous bond fission on hydrogenation was recently reported.[29] Delcosine diacetate was converted into the pinacolone (35). Hydrogenation of this over platinum gave the seco-compound (37), presumably by way of an immonium ion (36).



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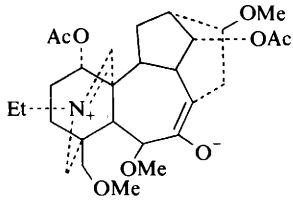
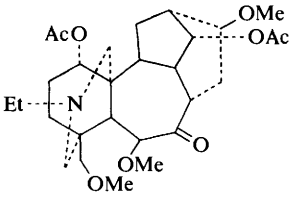


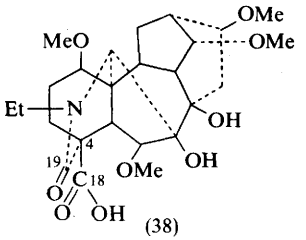
(36)

[29] T. Amiya and T. Shima, *Bull. Chem. Soc. Japan*, 1967, **40**, 1957.



(37)

Bredt's Rule Limitations. The decarboxylation[21] of lycoctonamic acid (38) and other reactions in which C-18 was lost[30] seemed to require transient formation of a 4,19 double bond. Ferris[31] and Büchi[32] have questioned this explanation in view of the likely angle strain involved (Bredt's rule) and have offered alternative explanations. Recent preparations of bicyclo[3,3,1]non-1-ene[33] (39) and studies



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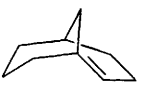
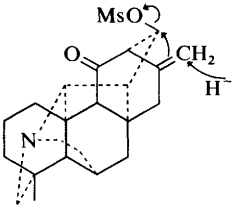


(39)

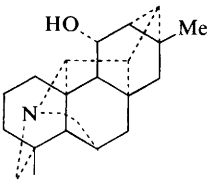
of β-keto-acid decarboxylation now make the earlier explanations plausible, if not mandatory. The double bonds in compounds such as (26) do not appear to be particularly strained, but the 8,15 double bonds of the 'pyro' derivatives (*e.g.* 28) are unusually reactive (see ref. 1, pp. 64, 65, 73, 78). This must be due to distortion from the normal valence angles.

Hetisine Reaction. In an attempt[34] to convert hetisine to kobusine the former was transformed into the mesylate (40). When this was treated with lithium aluminium hydride the mesylate was removed as expected but the exocyclic methylene group was replaced by a deshielded methyl group on quaternary carbon (δ 1.18). The product appeared to be the cyclopropane derivative (41), since oxidation of the hydroxy-group gave a ketone with ν_{max} 1680 cm^{-1} and λ_{max} 204 nm (ε5400). This was confirmed by an *X*-ray analysis of the methiodide of (41). The authors suggest that co-ordination of the mesylate groups with some aluminium species assists the process illustrated in (40).

[30] O. E. Edwards, L. Marion, and D. K. R. Stewart, *Canad. J. Chem.*, 1956, **34**, 1315.
[31] J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, 1966, **88**, 3522.
[32] G. Büchi, personal communication.
[33] [a] J. A. Marshall and H. Fauble, *J. Amer. Chem. Soc.*, 1970, **92**, 948; [b] R. Wiseman and W. A. Pletcher, *ibid.*, p. 956.
[34] H. E. Wright, G. Newton, and S. W. Pelletier, *Chem. Comm.*, 1969, 507.

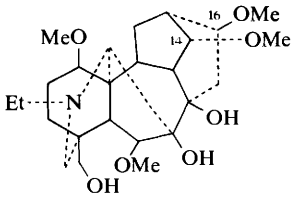


(40)

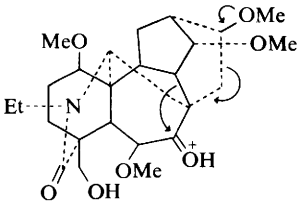


(41)

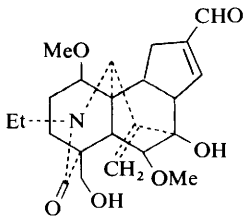
Lycoctamone. Among the most unusual aspects of lycoctonine chemistry was the rearrangement of the lactam (42), apparently *via* the pinacolone (43), to an $\alpha\beta$-unsaturated carbonyl compound, lycoctamone, with the overall loss of water, methanol, and the methyl of one methoxy-group. By a process of elimination using several alkaloids of the family and lycoctonine transformation products, the two methoxy-groups involved were shown to be those on C-14 and C-16. N.m.r. spectroscopy and other evidence showed the presence of an aldehyde group conjugated with a trisubstituted double bond, an exocyclic methylene group, and a tertiary hydroxy-group. On this basis and mechanistic considerations, structure (44) was proposed for lycoctamone.[35] The production of the



(42)



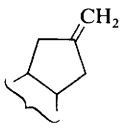
(43)



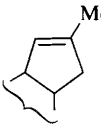
(44)

three olefins (45), (46), and (47) and the cyclopentanone (48) uniquely located the aldehyde function on the five-membered ring. Hydrogen-bonding in the derived ketone (49) placed the original trisubstituted double bond in relation to the

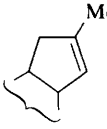
[35] M. H. Benn, J. D. Connolly, O. E. Edwards, L. Marion, and Z. Stojanac, *Canad. J. Chem.*, 1971, **49**, 425.



(45)



(46)



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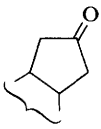

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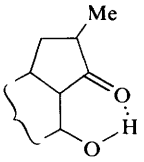
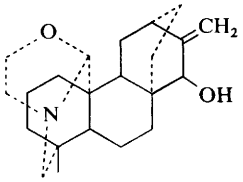


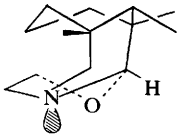
(49)

tertiary hydroxy-group. The presence of the allyl alcohol system and its relation to the nitrogen were shown by oxidation studies and n.m.r. spectroscopy. Hence the assigned structure rests on firm ground. Since several carbon atoms become readily accessible in lycoctamone and its analogues from related alkaloids, they may be useful in biosynthetic studies.

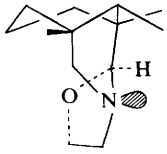
Atisine Conformation or Configuration. An interesting controversy has developed over the origin of an apparently split methyl signal in the n.m.r. spectrum of atisine (50) in aprotic solvents. Pelletier and Oeltman[36] suggested that this corresponds to the two conformations (51) and (52). The coalescence temperature



(50)

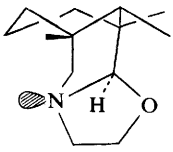


(51)

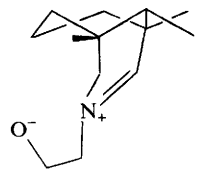


(52)

(85 °C) corresponded to an activation energy of *ca.* 20 kcal mol^{-1} for their equilibration. Pradhan and Girijavallabhan[37] challenged this interpretation since the energy barrier is abnormally large for nitrogen inversion. They observed that the 20-hydrogen gave rise to two signals with intensity ratio roughly 2:1. They attributed both this and the splitting of the methyl signal to the presence of two 20-epimers (51) and (53) (conformation not defined) in aprotic solvents. Addition of D_2O to an [$^2H_6$] acetone solution of atisine eliminated the extra 'methyl' signal and broadened the 20-hydrogen signals. This effect was attributed to lowering of the activation energy of formation of the ionic intermediate (54) between (51) and (53).



(53)



(54)

[36] S. W. Pelletier and T. N. Oeltman, *Tetrahedron Letters*, 1968, **24**, 2019.
[37] S. K. Pradhan and V. M. Girijavallabhan, *Chem. Comm.*, 1970, 644.

The American workers' assignment of conformation is open to question since the precise angular dependence of nitrogen anisotropy is uncertain (*e.g.* unusually large shieldings have been observed[38]). The Indian workers' criticism on energetic grounds is also valid. On the other hand, the conclusions of the latter are subject to two criticisms: (1) the configuration (53) is improbable because of large oxygen–hydrogen interactions; (2) the origin of the 20-hydrogen doublet was not rigorously related to the same phenomenon since the signals broadened but did not approach each other or coalesce as protic solvent was added or the temperature raised. Neither group of authors mention the location of the 15-hydroxyl signal in the n.m.r. spectrum of atisine, or its removal by deuterium exchange before the observations in aprotic solvents.*

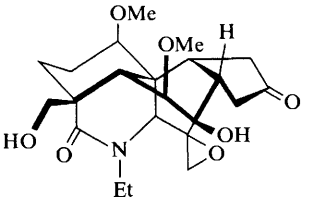
Spectral Anomalies. The unusual spectra of the pyro-derivatives of the aconitine group of alkaloids were discussed earlier. It is interesting to note that strained double bonds do have some bathochromic shift of their u.v. absorption, *e.g.* (39) has λ_{max} 206 nm, ε7500[33b].

The effect on the u.v. and i.r. spectra due to trans-spatial carbonyl interactions was first noted[39] in the diterpenoid alkaloids in 1954. Comparable observations in the chemistry of delpheline[40] were followed by a study of carbonyl–olefin interactions.[41] Subsequently, a number of cases of the last type of interaction were recognised in diterpenoid alkaloids. Delnudine (8) has a $\beta\gamma$-unsaturated carbonyl system, and the $n\pi^*$ band is shifted to 300 nm, with a moderately enhanced log ε of 1.76. The *X*-ray analysis[12] showed the carbonyl carbon and nuclear double bond carbon to be 2.90 Å apart, with the plane of the two double bonds inclined at 34°.

Hetidine (5) has unusual short-wavelength absorption (λ_{max} 209 nm, ε 5200) probably due to trans-spatial interaction, but the $n\pi^*$ band was not reported. Songoramine (6) had λ_{max} 295 nm, log ε 2.60, which gave an important guide to proximity of the carbonyl group and double bond. The angle between the carbonyl and double bond axes (Dreiding models) is approximately 82°, the directions of the π-orbitals intersect at a 75° angle, and the nuclear carbons are nearly 2.5 Å apart. In the case of miyaconitine (1) the same inference was drawn from the absorption with λ_{max} 288 nm, log ε 2.6. The distance between the carbonyl carbon and nuclear double bond carbon is estimated to be 2.5 Å, the angle between the bond axes 45°, and the π-orbitals nearly orthogonal (85°). An interesting i.r. interaction was noted in the case of songoramine. The carbonyl frequency was abnormally high (1722 cm^{-1}) but shifted to 1690 cm^{-1} when the double bond was reduced. This effect is much larger than could be expected for a release of angular distortion. Trans-spatial interactions were invoked in lycoctamone chemistry[35] to account for the abnormally long wavelength of the

[38] M. Wiewiorowski, O. E. Edwards, and M. D. Bratek-Wiewiorowska, *Canad. J. Chem.*, 1967, **45**, 1447.
[39] O. E. Edwards and L. Marion, *Canad. J. Chem.*, 1954, **32**, 195.
[40] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 1956, 3121.
[41] R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 1956, 2302.

* Prof. Pradhan has kindly informed the author that the exchange was done in their work.



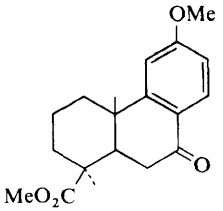
(55)

π–π^* band of the cyclopentenone system (245 nm) and the low carbonyl stretching frequency in the epoxy-ketone (55) (1730 cm^{-1}).

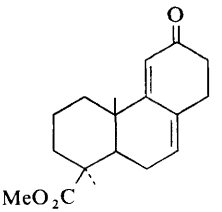
pK_a *Values.* The literature on diterpenoid alkaloids contains many examples of the effect of carbonyl groups on the basic strength of nitrogen.[42] The phenomena result from inductive effects through bonds and/or effects through space. A recent use[11] of these effects was in approximately locating the secondary hydroxy-group of delnudine (8). A drop in pK_a of two units in going from delnudine to the corresponding diketone required that this hydroxy-group be in ring A or ring B. Since four bonds separate the carbonyl carbon from the nitrogen, the effect must be largely trans-spatial in character.

A marked effect of the 11-ketone in spiradine A (15) is interesting. Its pK_a is 8.35 while that of the 11-alcohol is 9.54. Acetylation of the hydroxyl again lowers the pK_a to 9.02 (all in 50% aqueous methanol).

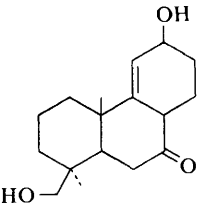
C. Synthesis.—*Atisine and Veatchine Types.* Zalkow and co-workers developed syntheses of intermediates potentially transformable into atisine-type alkaloids, starting with podocarpic acid. The general approach is illustrated by a synthesis[43] of an ajaconine degradation product. Methyl *O*-methyl-7-keto-podocarpate (56) was reduced to the diol, which was converted by Birch reduction to dienone (57). The diene diol diacetate from this was converted to the 7,8-epoxide. Boron trifluoride converted this to the non-conjugated enone (58) which isomerised and



(56)



(57)

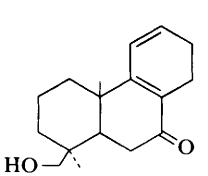


(58)

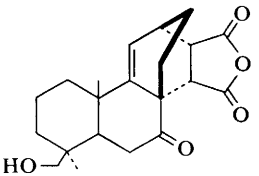
[42] O. E. Edwards, *Chem. in Canada*, 1961, **13**, 40; D. Dvornik and O. E. Edwards, *Canad. J. Chem.*, 1964, **42**, 137.

[43] L. H. Zalkow, B. Kumar, D. H. Miles, J. Nabors, and N. Schnautz, *Tetrahedron Letters*, 1968, 1965.

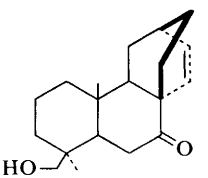
dehydrated on alumina to give (59). On treatment with maleic anhydride (59) gave two adducts, one of which (60) was converted to an unsaturated ketone assigned structure (61) by reference to the previously known 7-deoxy-compound.



(59)

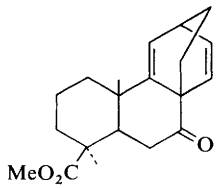


(60)

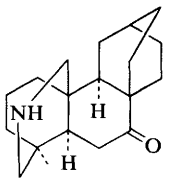


(61)

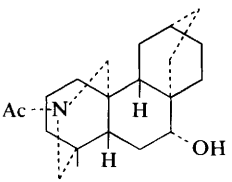
A recent paper[44] describes further conversion of (60). The corresponding keto-tricarboxylic acid was converted to the monoester and this was bisdecarboxylated to the diene (62). Catalytic reduction and formation of the heterocyclic ring by the well-known acyl azide photolysis[45] gave ketolactam (63). This was transformed into the enantiomer of the known degradation product (64).



(62)

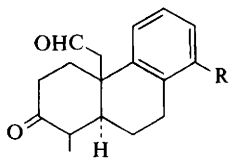


(63)

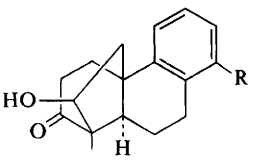


(64)

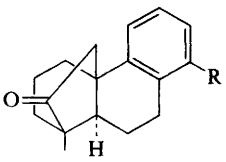
Matsumoto and co-workers[46] succeeded in obtaining the desired cyclisation of the Turner intermediate[47] (65; R = H or OMe) into (66). The carbonyl group was removed from (66) by the dithioketal procedure and the product converted to the ketone (67). Nitrosation of the ketone followed by Beckmann rearrange-



(65)



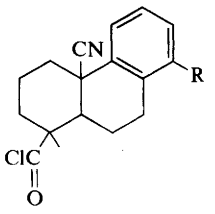
(66)



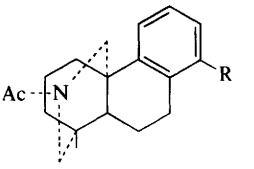
(67)

[44] J. Nabors, H. Miles, and L. H. Zalkow, *Tetrahedron Letters*, 1969, 2445.
[45] 'Nitrenes,' ed. W. Lwowski, Interscience Publishers, New York, 1970, Chapter 7.
[46] T. Matsumoto, M. Yanagiya, E. Kawakami, T. Okuno, M. Kakizawa, S. Yasuda, Y. Gama, J. Omi, and M. Matsunaga, *Tetrahedron Letters*, 1968, 1127.
[47] R. B. Turner, G. B. Diana, G. E. Fodor, K. Gerbert, D. L. Simmons, A. S. Rao, O. Roos, and W. Wirth, *J. Amer. Chem. Soc.*, 1966, **88**, 1786.

ment of the α-oximino-ketone gave the cyano-acid chloride (68). This was readily converted into the *N*-acetyl derivatives (69; R = H or OMe) which had previously been transformed into *Garrya* alkaloids.[48]

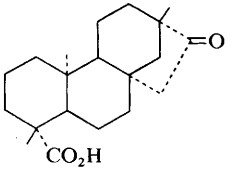


(68)

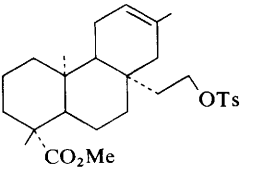


(69)

Coates and Bertram[49] developed a π-route to usefully substituted compounds potentially convertible by the acyl azide procedure[45] to atisine derivatives. Isosteviol (70) was converted to the unsaturated tosylate (71). Buffered formolysis

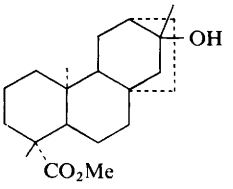


(70)

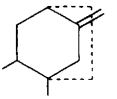


(71)

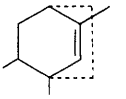
of (71) gave the tetracyclic alcohol (72) which could be dehydrated to a mixture of olefins (73) and (74) with atisene and isoatisene skeletons respectively. Since



(72)



(73)

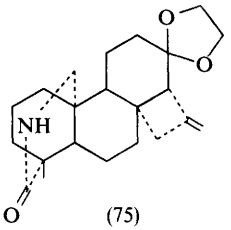


(74)

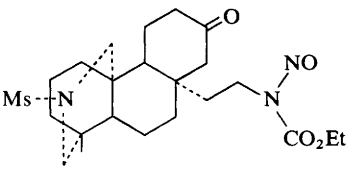
steviol has been synthesised,[50] this work has the potential of total synthesis. Wiesner, Valenta, and co-workers[51] have published a modification of their atisine syntheses, leading formally to a synthesis of veatchine. The intermediate (75) from the earlier synthesis was converted in a series of steps to the nitroso-urethane

[48] A. Tahara and K. Hirao, *Tetrahedron Letters*, 1966, 1453; R. W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, *ibid.*, 1965, 2945.
[49] R. M. Coates and E. F. Bertram, *Chem. Comm.*, 1969, 797.
[50] K. Mori, Y. Nakahara, and M. Matsui, *Tetrahedron Letters*, 1970, 2411.
[51] K. Wiesner, S. Uyeo, A. Philipp, and Z. Valenta, *Tetrahedron Letters*, 1968, 6279.

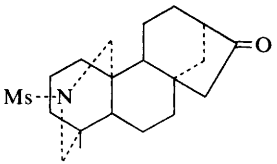
(76). Sodium ethoxide in refluxing ethanol transformed (76) into the diazo-compound, which decomposed immediately. The carbene 'inserted' into the



(75)



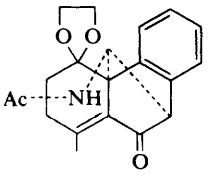
(76)



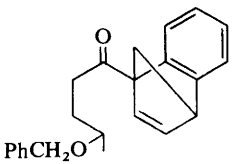
(77)

12,13 bond to give (77) in 65% yield. (77) Was converted into the corresponding *N*-acetyl ketone which had previously[52] been converted into veatchine. The overall synthesis of veatchine has now been given final authenticity by resolution of the alcohol corresponding to (77) as its half ester with succinic acid.[53] One enantiomer gave an optically active form of (77) which proved identical to a degradation product of veatchine with the same structure.

In a model study for the synthesis of hexacyclic alkaloids of songorine type the amide (78) has been synthesised.[54] The key reactions were the formation of



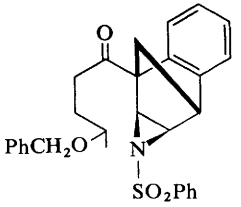
(78)



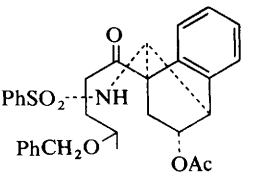
(79)

the aziridine (80) by reaction of the double bond of (79) with benzenesulphonyl azide, and rearrangement of (80) to (81) in hot acetic acid. This rearrangement has precedent in the norbornylene series,[55] although the question of which bond

[52] R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. Wiesner, *Coll. Czech. Chem. Comm.*, 1966, **31**, 602.
[53] K. Wiesner, Z. T. Komlossy, A. Philipp, and Z. Valenta, *Experientia*, 1970, **26**, 471.
[54] K. Wiesner, A. Philipp, and Pak-tsun Ho, *Tetrahedron Letters*, 1968, 1209.
[55] L. H. Zalkow and A. C. Oehlschlager, *J. Org. Chem.*, 1963, **28**, 3303.

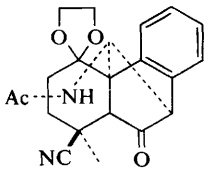


(80)

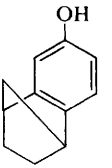


(81)

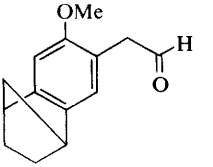
would migrate is *a priori* hard to judge. A series of conventional reactions converted (81) into (78). Contrary to the original conclusions[54] the subsequent steps were abortive. An *X*-ray crystallographic study[56] showed that addition of cyanide ion to the enone system of (78) gave the undesired configuration (82).



(82)

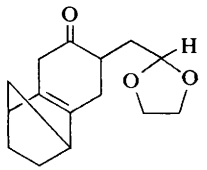


(83)

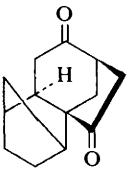


(84)

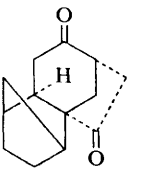
In exploration of routes aimed at completing the carbocyclic system by the above general synthetic approach, a study of phenol (83) has been made.[57] Rearrangement of the allyl ether of (83), methylation and oxidation gave the aldehyde (84). Birch reduction of the ethylene ketal of (84) led to the non-conjugated enone (85). Acid-catalysed cyclisation of this followed by hydrogenation and oxidation gave a diketone tentatively assigned configuration (86). Basic isomerisation of (85) to the conjugated enone, removal of the blocking group,



(85)



(86)

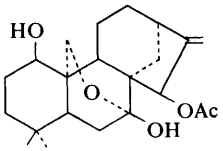


(87)

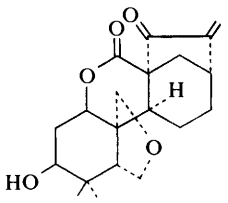
cyclisation, hydrogenation, and oxidation gave an isomeric diketone. Its configuration was proven to be as in (87) by *X*-ray crystallography. Unfortunately, the enones corresponding to (86) and (87) were not compared.

[56] K. B. Birnbaum, *Tetrahedron Letters*, 1969, 1071.
[57] K. Wiesner, A. Deljac, and T. Y. R. Tsai, *Tetrahedron Letters*, 1970, 1145.

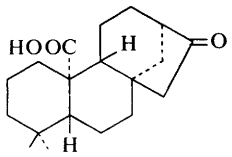
Fujita and co-workers[58] have converted the diterpenes trichokaurin (88) and enmein (89) into the keto-carboxylic acid (90), which had earlier been transformed into atisine and veatchine.[59] The 1-mesylate of trichokaurin was oxidised to the



(88)

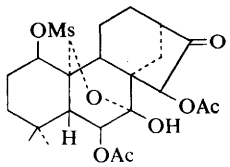


(89)

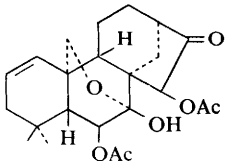


(90)

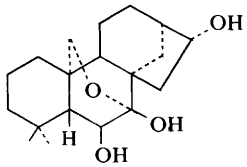
norketone (91). When this was heated (150 °C) in dimethyl sulphoxide the olefin (92) was formed. The double bond was reduced catalytically, then the acetoxy-group adjacent to the ketone carbonyl group removed by calcium–ammonia reduction, giving the triol (93) and the corresponding 16-ketone. Modified Wolff–Kishner reduction of (93), followed by hydrogenation, removed the ring B substituents. The product was oxidised by the Jones reagent to the desired (90).



(91)

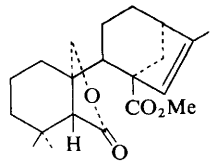


(92)

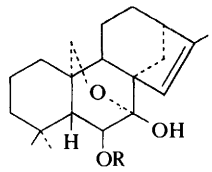


(93)

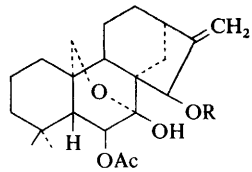
Enmein (89) had previously been converted into the unsaturated lactone-ester (94). Acyloin cyclisation of this gave the desired hemiketal (95; R = H) in 50% yield. Photo-oxidation of its monoacetate (95; R = Ac) gave the allylic alcohol (96) in 72% yield. Selective blocking of (96; R = H) was achieved using acetic



(94)



(95)



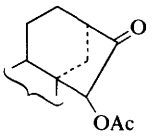
(96)

[58] E. Fujita, T. Fujita, and H. Katayama, *Tetrahedron*, 1970, **26**, 1009; E. Fujita, T. Fujita, and M. Shibuya, *ibid.*, 1969, **25**, 2517.

[59] S. Masamune, *J. Amer. Chem. Soc.*, 1964, **86**, 290, 291.

anhydride and sodium acetate in refluxing chloroform. The resulting diacetate (96; R = Ac) was cleaved by ozone to (97). Calcium in ammonia converted this to (93) which had been obtained from trichokaurin.

A formal total synthesis of veatchine was achieved by Turner and co-workers.[60] The vinyl group of (98) was converted to the epoxide. The action of potassium t-butoxide on this cyclised it to (99). The double bond was reduced catalytically



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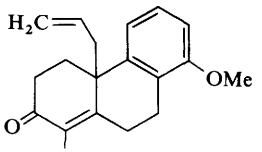
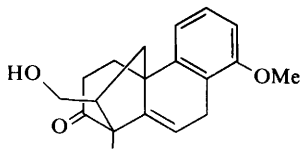
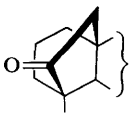


(98)

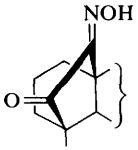


(99)

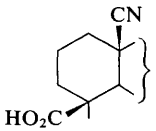
giving the 5α-isomer, then the carbonyl group removed by Wolff–Kishner reduction. The hydroxymethyl group was removed by oxidation to the aldehyde, and ozonolysis of its enol acetate, giving the cyclopentanone (100). Treatment of (100) with butyl nitrite and potassium t-butoxide converted it to the oximino-ketone (101). The oxime tosylate readily rearranged to the cyano-acid (102).



(100)

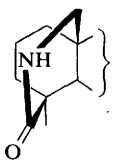


(101)

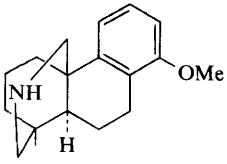


(102)

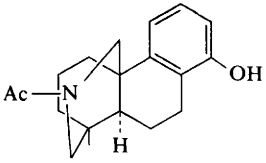
Lithium aluminium hydride reduction of (102) gave lactam (103), and under more vigorous conditions the base (104). The structure and stereochemistry of this was confirmed by comparison of it and the corresponding *N*-acetylphenol (105) with Valenta and Wiesner's intermediate on the route to veatchine.[61]



(103)



(104)

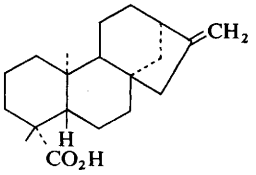


(105)

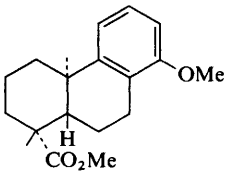
[60] P. Grafen, K. J. Kabbe, O. Roos, G. D. Diana, Tsung-tee Li, and R. B. Turner, *J. Amer. Chem. Soc.*, 1968, **90**, 6131.

[61] Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 1964, 2437.

Another potential route to veatchine was developed by Mori and Matsui.[62] They synthesised (±)-kaur-16-en-19-oic acid (106) starting with (107), which had

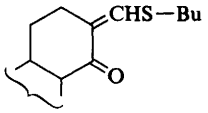


(106)

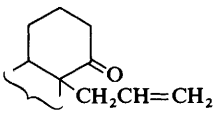


(107)

been prepared by two pathways. The five-membered bridge was added by transforming (107) into the ketone (108) with C-13 protected. An allyl group was introduced at C-8 to give (109). This was converted into the desired skeleton by well-known methods.

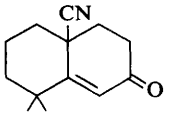


(108)

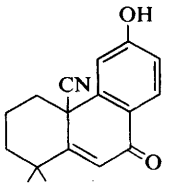


(109)

An approach to the polycyclic diterpenes, including veatchine, was initiated by Meyer.[63] 2,2-Dimethylcyclohexanone was converted to the cyano-enone (110). This was elaborated into the cyano-phenol (111) which has potential for the synthesis of the alkaloids.



(110)



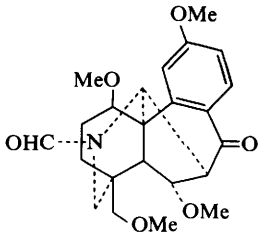
(111)

Aconitine Type. In an ingenious set of interpretations, Büchi and Wiesner and their co-workers[27] showed that the chemistry of aconitine and delphinine was consistent with a lycoctonine skeleton for these alkaloids. However, to provide a rigorous structure proof, synthesis of some of the unusual degradation products seemed desirable. (An *X*-ray crystallographic analysis of desmethanol aconinone

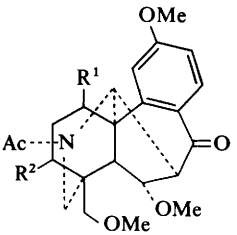
[62] K. Mori and M. Matsui, *Tetrahedron*, 1968, **24**, 3095.
[63] W. L. Meyer, R. W. Huffman, and P. G. Schroede, *Tetrahedron*, 1968, **24**, 5959.

hydriodide[64] and the interrelation of aconitine and delphinine[65] established that the structures were correct.) The missing ring A stereochemistry was provided by Büchi and co-workers[66] and by Wiesner and co-workers.[67]

The major synthetic effort in this area has been directed at the partially aromatic degradation products such as (112) from delphinine. A synthesis of a racemic model compound (113; $R^1 = R^2 = H$) was recently presented in detail[68] and correlation of this[69] with an optically active product from aconitine (113; $R^1 = OMe$, $R^2 = OH$) was described. This confirmed the structure of this degradation product and completed a purely chemical proof of the alkaloid



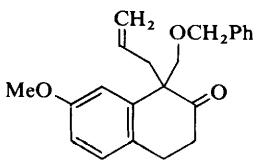
(112)



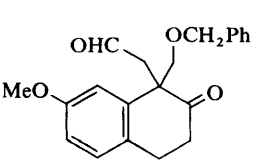
(113)

skeleton and substitution pattern. Since (±)-(112) has now been synthesised[70] by a very similar route and correlated with the degradation product of delphinine,[71] only the latter synthesis will be described.

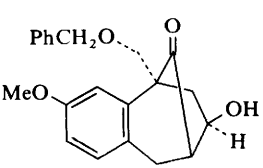
7-Methoxy-2-tetralone was substituted successively by allyl and benzyloxymethylene groups giving (114). The double bond was hydroxylated, then the glycol cleaved, producing the keto-aldehyde (115). This was cyclised to the hydroxy-ketone (116) then the carbonyl converted to the ethylene ketal. The



(114)



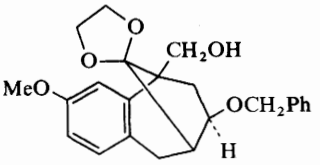
(115)



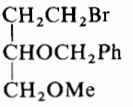
(116)

[64] M. Przybylska and L. Marion, *Canad. J. Chem.*, 1959, **37**, 1116.
[65] K. Wiesner, D. L. Simmons, and L. R. Fowler, *Tetrahedron Letters*, 1959, No. 18, 1.
[66] F. W. Bachelor, R. F. C. Brown, and G. Büchi, *Tetrahedron Letters*, 1960, No. 10, 1.
[67] K. Wiesner, D. L. Simmons, and R. H. Wightman, *Tetrahedron Letters*, 1960, No. 15, 23.
[68] K. Wiesner, Wen-Ling Kao, and J. Santroch, *Canad. J. Chem.*, 1969, **47**, 2431.
[69] K. Wiesner, Wen-Ling Kao, and E. W. K. Jay, *Canad. J. Chem.*, 1969, **47**, 2734.
[70] K. Wiesner, E. W. K. Jay, C. Demerson, T. Kanno, J. Krepinsky, L. Poon, T. Y. R. Tsai, A. Vilim, and C. S. Wu, *Experientia*, 1970, **26**, 1030.
[71] K. Wiesner, M. Gotz, D. L. Simmons, and L. R. Fowler, *Coll. Czech. Chem. Comm.*, 1963, **28**, 2462.

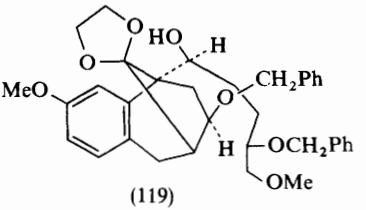
relative configuration of the hydroxy-group followed from the fact that borohydride reduction of the corresponding ketone gave the epimeric alcohol. A multistep manipulation of the blocking groups gave the benzyl ether (117). The side-chain was extended by reaction of the aldehyde derived from (117) with the Grignard reagent from the protected bromo-diol (118). Only one epimer (119)



(117)

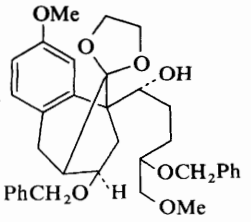


(118)

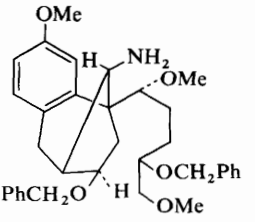


(119)

was produced. This was demonstrated to have the unnatural configuration by completion of the synthesis, hence the epimer (120) had to be prepared by oxidation and lithium aluminium hydride reduction. The hydroxy-group was now methylated and the ketal hydrolysed. The carbonyl was converted to an amino-group by reductive amination. The desired isomer (121) was obtained nearly

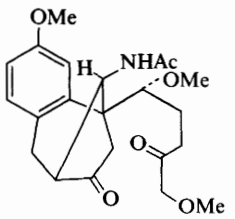


(120)

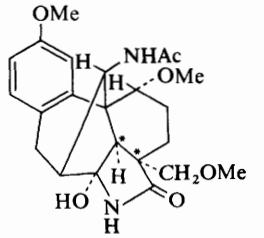


(121)

quantitatively. Acetylation, hydrogenolysis of the benzyl blocking group and oxidation converted (121) into the diketone (122). Potassium cyanide in refluxing ethanol cyclised (122), and by cyanide addition to the enone and partial hydrolysis converted it directly into (123). Fortunately, the desired stereochemistry at the

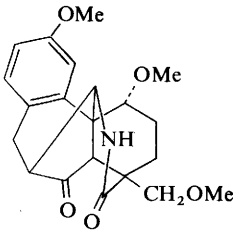


(122)

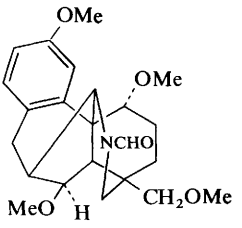


(123)

starred centres resulted, a fact which became evident when treatment of (123) with acid gave the keto-lactam (124). Lithium aluminium hydride converted (124) into a mixture of epimeric amino-alcohols. By recycling through the ketone a 58% yield of the desired epimer was obtained. This was methylated, then oxidised with permanganate to the formyl derivative (125). Finally, Jones oxidation of the benzylic methylene produced the degradation product (112). This and the corresponding secondary amine and *N*-acetyl derivative had identical solution spectra and chromatographic behaviour to the compounds derived from delphinine. It is hoped that these compounds can be used as relays in a total synthesis of the alkaloid.

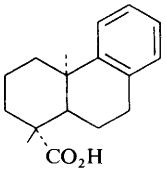


(124)

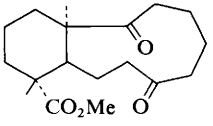


(125)

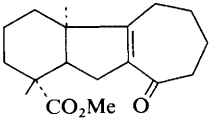
Tahara and Ohsawa[72] have developed an approach which could lead to the lycoctonine skeleton. Although the diketo-ester (127) derived from *enantio*-deoxypodocarpic acid (126) cyclises to the linear system (128),[73] introduction of



(126)

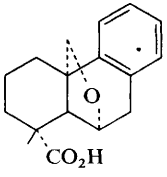


(127)

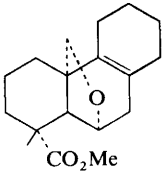


(128)

an oxygen bridge as in (129) redirects the cyclisation. Acid (129) derived from (−)-abietic acid[74] was reduced by lithium–ethylamine–t-amyl alcohol to (130).



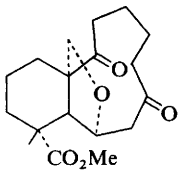
(129)



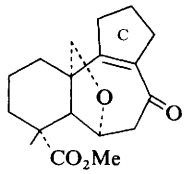
(130)

[72] A. Tahara and T. Ohsawa, *Tetrahedron Letters*, 1969, 2469.
[73] A. Tahara, O. Hoshino, and T. Ohsawa, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 54.
[74] A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron*, 1965, **21**, 2133.

The methyl ester of (130) was hydroxylated, and the resulting diol cleaved to give the diketone (131). Acid cyclisation of (131) gave 80% of the angular enone (132). The structural assignment was based on a spin-decoupling n.m.r. study of the 6-proton of (132) and the corresponding dihydro-compound. Since the hetero-cyclic system and bridge from the hetero-ring to ring B could easily be made from (132), the major problem in this route is the introduction and carrying of a ring C substituent.

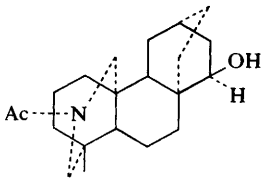


(131)

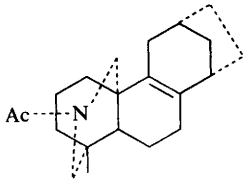


(132)

The challenge of effecting in the laboratory the rearrangement from an atisine to a lycoctonine skeleton is very relevant for both partial and total synthesis. Attempts to do this by solvolysis of derivatives with either configuration at C-15 of compounds derived from atisine[75] had given products with the wrong skeleton (*e.g.* 133 → 134). However, Johnston and Overton[76] have found that pyrolysis

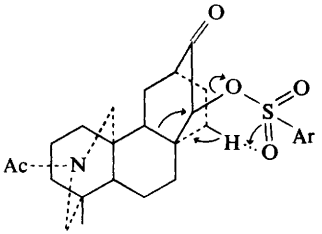


(133)

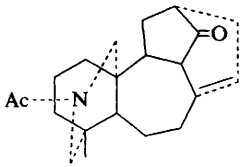


(134)

of a 15-tosylate (135) with the atisine configuration (presumably 15α) led in good yield to the 8,15-olefin (136). The structure of (136) was confirmed by an *X*-ray



(135)



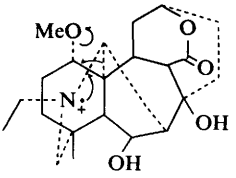
(136)

[75] S. W. Pelletier and A. Ichihara, *Chem. and Ind.*, 1967, 2149.
[76] J. P. Johnston and K. H. Overton, *Chem. Comm.*, 1969, 329.

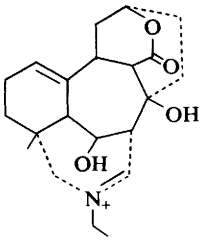
analysis.[77] It was suggested that the favourable geometry of the transition state illustrated in (135) directed the rearrangement.

The major problem left in a formal total synthesis of the lycoctonine skeleton is the movement of the 8,15 double bond to the 7,8 position. W. A. Ayer and co-workers[78] have also achieved an atisane to aconane rearrangement.

D. Mass Spectra.—The first contribution to interpretation of the mass spectra of these alkaloids was by Pelletier and Aneja.[79] They examined the fragmentation of heteratisine (137) and related bases. The dominant process, as has since proven to be general, was loss of the 1-methoxy-group to give ion (138). The transition

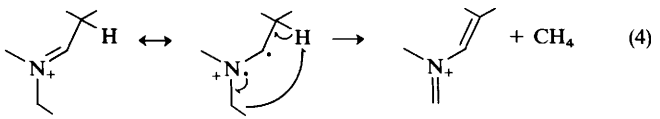


(137)



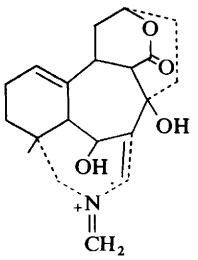
(138)

was confirmed by accurate mass measurement and observation of a metastable peak. Similar evidence confirmed the loss of methane from (138). The resulting ion was formulated as (139) and its formation considered to be as in equation 4.

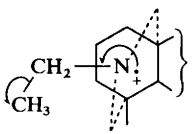


(4)

The loss of a methyl group from the parent ion was also noted. This was also considered to come from the *N*-ethyl group [see (140)]. However, the work of



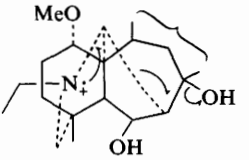
(139)



(140)

[77] G. Ferguson and J. P. Johnston, *Chem. Comm.*, 1969, 330.
[78] Personal communication from Prof. W. A. Ayer.
[79] S. W. Pelletier and R. Aneja, *Tetrahedron Letters*, 1967, 557.

Yunusov described below suggests that these interpretations be treated with caution. The fragmentation illustrated in (141) takes place, but is not as important

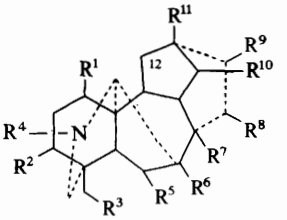


(141)

as might have been expected (intensity 10 for $M-17$). Elimination of water from the parent and intermediate ions is a significant event (intensity 9 to 19). Comparison with these and other fragmentations was used to interpret the mass spectra of three new lactone alkaloids from *A. heterophyllum* and to help in assigning structures to them.

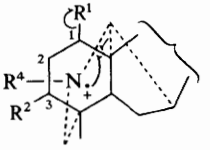
Yunusov and co-workers have analysed the mass spectra of some of the lycoctonine–aconitine family of alkaloids[80] and of songorine, its derivatives, and songoramine.[81]

For the bases with a lycoctonine skeleton (142) the base peak usually corresponded to loss of the 1-substituent as a radical. If a 3-substituent was present

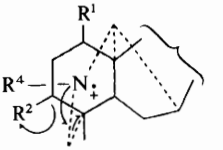


(142)

as in many of the aconitine group, the hetero-ring fragmented in two ways, (142a) and (142b). These paths were confirmed by the presence of metastable peaks.



(142a)



(142b)

For the aconitine group (142; R^6 = H, R^7 = OH) loss of the 8-substituent (R^7) was important. If R^7 was OMe or OCOMe, the base peak corresponded to loss of R^1 and methanol or acetic acid respectively.

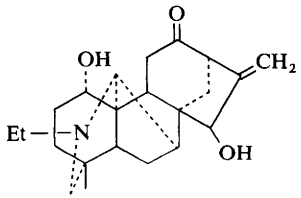
[80] M. S. Yunusov, Ya. V. Rashkes, V. A. Tel'nov, and S. U. Yunusov, *Khim. prirod. Soedinenii*, 1969, 515.

[81] M. S. Yunusov, Ya. V. Rashkes, S. Yu. Yunusov, and A. S. Samatov, *Khim. prirod. Soedinenii*, 1970, 101.

The lycoctonine group ($R^6 = R^7 = OH$) lose water to a small extent. However, in lycoctonine monoacetate ($R^3 = OCOMe$) the dehydration of both the parent ion (intensity 90) and the $M - 31$ ion (intensity 53) was markedly enhanced. An interesting intense peak from this monoacetate at $M - 137$ (relative intensity 68) was attributed to loss of methyl acetate from C-4, the 1-methoxyl as a radical, and possibly the 6-methoxy-group as methanol. However, this seems implausible and the origin of the peak needs more study. The intensity of these secondary peaks seemed sensitive to inlet temperature.

The loss of CH_3 ($M - 15$) noted by Pelletier and Aneja[79] was evident. It actually gave the base peak in the case of 1-deoxycondelphine. In the 19-oxo lactams derived from the alkaloids, in which the hetero-ring rupture is impeded, the $M - 15$ peak became the base peak. Contrary to the suggested loss of the methyl group from the *N*-ethyl group,[79] the *N*-desethyl and *N*-desethyl-*N*-methyl derivatives that were studied gave the same intense peak. The Russian workers suggested that the methyl radical came from C-12.

Songorine (143) and many of its derivatives gave the parent ion as base peak. The loss of the 1-substituent also took place, but the fragmentation gave a greater

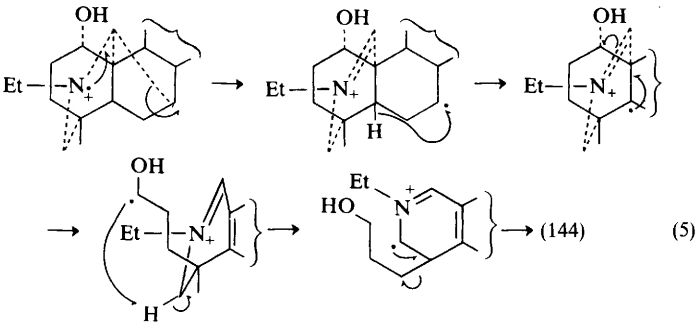


$M = 357$

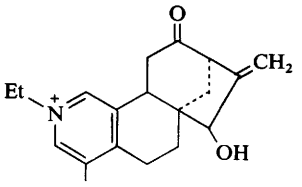
(143)

variety of important peaks than did the lycoctonine family. A weak $M - 15$ peak now appeared to arise from the *N*-ethyl group, since it was nearly absent in the spectrum of the *N*-desethyl analogue.

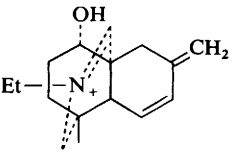
Only a few interesting fragmentations can be described because of space limitation. The loss of part of ring A was an important process. A possible route to *m/e* 298 is shown in equation 5, the structure (144) of the ion being modified from that suggested by Yunusov.



(5)

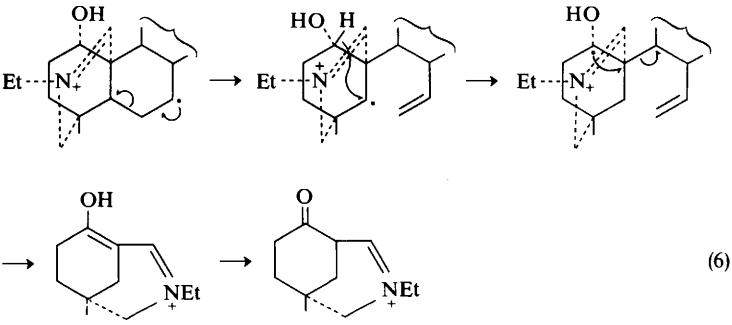


(144)



(145)

Loss of rings C and D was also observed. An alternative structure for the ion with *m/e* 180 is given in equation 6. Metastable peaks were observed corre-

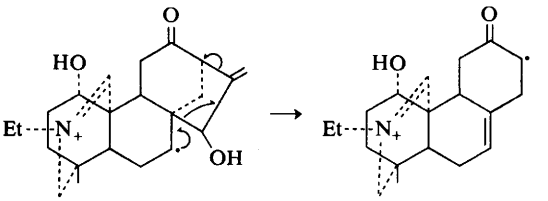


(6)

m/e 180

sponding to direct formation of this ion, and one with *m/e* 248 which was assigned structure (145).

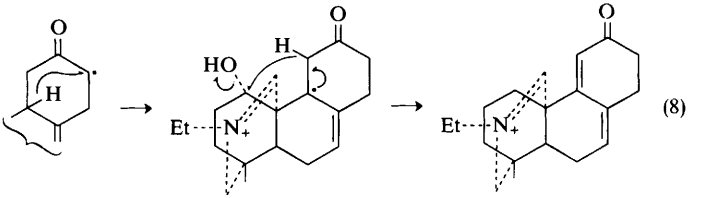
For dihydrosongorine an important fragmentation was postulated to involve loss of ring D (equation 7). An unusual process, if correctly formulated, involves



(7)

m/e 301

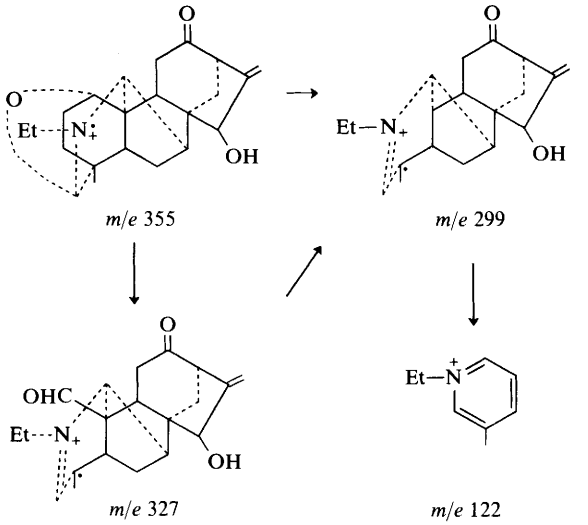
9 → 13 hydrogen transfer, followed by displacement of the 1-hydroxy-group (acetoxy) by a hydrogen atom from C-11 (see equation 8). Metastable peaks were observed for both transitions.



(8)

m/e 284

For songoramine an interesting fragmentation (Scheme 1) was proposed, and supported by the observation of metastable peaks where indicated.



Scheme 1

Deuterium labelling of the hydroxy-groups and exocyclic methylene group (not detailed in the text) was used to check some assignments for songorine and dihydrosongorine. It would seem advisable also to check these by accurate mass determination.

Waller and co-workers[82] have used g.l.c.–mass spectrum combination in studies of diterpenoid alkaloid synthesis in *Delphinium* plants.

E. Biosynthesis and Biogenetic Speculation.—The biosynthetic work with diterpenoid alkaloids has been only of preliminary nature.

Herbert and Kirby[83] found that [2-^{14}C]mevalonate fed through the cut stem of excised leaves of *D. elatum* was not significantly incorporated into delpheline.

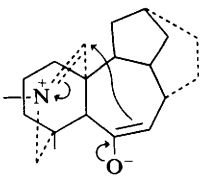
[82] S. D. Sastry, G. R. Waller, and H. Bunstrom, American Chem. Soc. Abstr. of Papers, 156th National Meeting, Sept., 1968, Biol. 20.
[83] E. J. Herbert and G. W. Kirby, *Tetrahedron Letters*, 1963, 1505.

The alkaloid was being synthesised in intact plants at the same stage of growth. Using the same feeding technique it was found that L-[*methyl*-^{14}C]methionine was incorporated into delpheline. Eighty-eight percent of the label entered methoxy-groups, 11% entered the *N*-ethyl group, but less than 5% was found in the methylenedioxy-group.

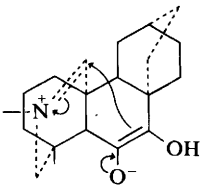
Benn and May[84] injected 1-^{14}C- and 2-^{14}C-labelled acetate and [2-^{14}C]-mevalonate into the stems of intact *D. brownii* just prior to blooming. The label was incorporated into lycoctonine and browniine to the extent of 0.002, 0.003, and 0.006% respectively.

Waller and co-workers[85] also used the stem injection method with intact *D. ajacis*. The incorporation into delcosine from [2-^{14}C]glycine was 0.09% (presumably into the *N*-ethyl group) and from [2-^{14}C]mevalonate was 0.04%. Neither group reported degradation to locate the labelled carbon.

There is a high order of probability that the atisine skeleton is an intermediate in the formation of the lycoctonine skeleton *in vivo*. Hence it was disturbing that solvolysis of derivatives of both 15-epimeric alcohols failed to give this rearrangement (see Section 2C). The major biogenetic controversy concerns the stage at which the 7–20 bridge is formed. Wiesner and Valenta[86] and Cookson and Trevett[40] postulated that aldol condensation was involved [see (146) and (147)

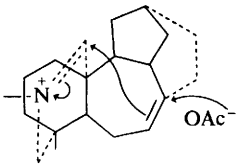


(146)

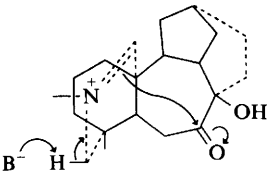


(147)

respectively]. Edwards[25] suggested that the bridging was the ultimate stage in the skeleton formation, occurring by a Prins-type cyclisation (148) (aconitine group) or by the cyclisation illustrated in (149) (lycoctonine group). Both these



(148)



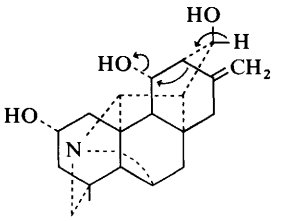
(149)

[84] M. H. Benn and J. May, *Experientia*, 1964, **20**, 252.
[85] G. M. Frost, R. L. Hale, G. R. Waller, L. H. Zalkow, and N. N. Girotra, *Chem. and Ind.*, 1967, 320.
[86] Z. Valenta and K. Wiesner, *Chem. and Ind.*, 1956, 354.

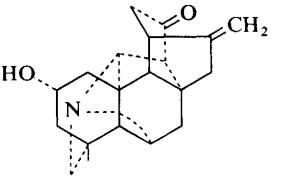
steps can be reproduced in the laboratory.[25,28] The occurrence of denudatine seems to support the aldol condensation route. However, the absence of activating oxygen on C-6, in the face of a general picture of progressive oxygenations in the plant, is disturbing. It seems possible that some alternative means of cyclisation is available to the plant for generating the bridge in denudatine and songorine (144) types.

The N–C-6 bridge found in hetisine, delnudine, miyaconitine *etc.* probably forms by displacement of a 6-β-pyrophosphate group. The facile formation of the bridge has already been demonstrated in ajaconine chemistry[87] and the mobile equilibrium between 6-keto-derivatives and the carbinolamines in hetidine (5), delnudine (8), and kobusine methiodide (9) attests to the strain-free nature of the hexacyclic skeleton.

The delnudine structure (8) represents a new skeletal variant. It was suggested[11] that it arises in the plant by rearrangement of hetisine (150) → (151) followed by oxidation to the carbinolamine.



(150)



(151)

Lappaconine (11) is the first bisnor (C_{18}) diterpene alkaloid to be found. The presence of the hydroxy-group on C-4 suggests that removal of C-19 is by a Baeyer–Villiger type process. The biosynthesis of the lactone alkaloids such as heteratisine (137) also may involve such a step.

The presence of a carbonyl at C-13 of miyaconitine led to the suggestion[4] that the 14–20 bridge forms by aldol condensation. However, as in the case of the 7–20 bridge of denudatine discussed above, many examples of this bridge occur without activating oxygen being present on C-13 in the final alkaloid (ref. 1, pp. 174—188).

3 *Daphniphyllum* Alkaloids

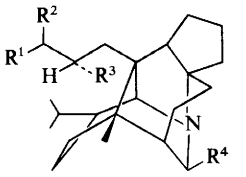
A. Structure.—The plant *Daphniphyllum macropodum* Miq. contains a great variety of related alkaloids (see Table). Three main N-heterocyclic skeletons occur, represented by daphniphylline (152), secodaphniphylline (156), and yuzurimine (157). Within the daphniphylline group, notable variations in the oxygen heterocycle occur in daphmacrine (154) and daphnimacropine (155). Macrodaphnine (161) is the *N*-oxide of yuzurimine. The structures of representative members

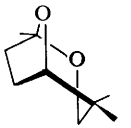
[87] D. Dvornik and O. E. Edwards, *Tetrahedron*, 1961, **14**, 54; **16**, 283.

Table 1

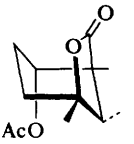
Alkaloid	*Ref.*	*Structure*	*Formula*	*m.p.* (°C)
Daphniphylline (daphniphyllamine)	*a*	(152)	$C_{32}H_{49}O_5N$	240 (B·HCl)
Codaphniphylline	*a*	(153)	$C_{30}H_{47}O_3N$	267 (B·HCl)
Daphmacrine	*b*	(154)	$C_{32}H_{49}O_4N$	>300 (B·HBr)
Daphnimacropine	*c*	(155)	$C_{31}H_{49}O_3N$	307 (B·MeI)
Daphmacropodine	*c*	—	$C_{32}H_{51}O_4N$	215
Secodaphniphylline	*d*	(156)	$C_{30}H_{47}O_3N$	130
Alkaloid D	*d*	—	$C_{30}H_{47}O_4N$	—
Yuzurimine (macrodaphnidine)	*e*	(157)	$C_{27}H_{37}O_7N$	253 (B·HCl)
Yuzurimine A	*f*	(158)	$C_{25}H_{35}O_5N$	252 (B·HCl)
Yuzurimine B	*f*	(159)	$C_{23}H_{33}O_3N$	284 (B·HCl)
Macrodaphniphyllamine	*c*	(160)	$C_{23}H_{33}O_4N$	153
Macrodaphnine	*g*	(161)	$C_{27}H_{39}O_7N$	181.5
Macrodaphniphyllidine	*c*	(162)	$C_{25}H_{35}O_4N$	306 (B·HBr)
Yuzurimine C	*d*	(163)	$C_{23}H_{29}O_5N$	187
Yuzurimine D	*d*	—	$C_{24}H_{32}O_5N$	195
Alkaloid A_1	*d*	—	$C_{23}H_{33}O_3N$	226 (B·MeI)
Alkaloid A_2	*d*	—	$C_{24}H_{37}O_4N$	230 (B·MeI)
Methyl homodaphniphyllate	*h*	(164)	$C_{23}H_{37}O_2N$	234 (B·HCl)
Methyl homosecodaphniphyllate	*i*	(165)	$C_{23}H_{37}O_2N$	103
Alkaloid C	*d*	—	—	195.5
Neoyuzurimine	*d*	—	—	198
Neodaphniphylline	*d*	—	—	244

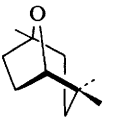
[a] H. Irikawa, N. Sakabe, S. Yamamura, and Y. Hirata, *Tetrahedron*, 1968, **24**, 5691. [b] T. Nakano, Y. Saeki, C. S. Gibbons, and J. Trotter, *Chem. Comm.*, 1968, 600. [c] T. Nakano and Y. Saeki, *Tetrahedron Letters*, 1967, 4791. [d] M. Toda, H. Irikawa, S. Yamamura, and Y. Hirata, *J. Chem. Soc. Japan*, 1970, **91**, 103. [e] H. Sakurai, N. Sakabe, and Y. Hirata, *Tetrahedron Letters*, 1966, 6309. [f] H. Sakurai, H. Irikawa, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1967, 2883. [g] T. Nakano and B. Nilsson, *Tetrahedron Letters*, 1969, 2883. [h] M. Toda, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1969, 2585. [i] H. Irikawa, M. Toda, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1969, 1821.

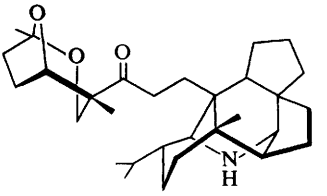


(152), R^1 =  ; $R^2 = O$; $R^3 = OAc$; $R^4 = H$

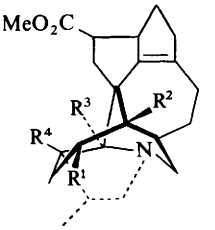
(153), R^1 as in 152; $R^2 = O$; $R^3 = R^4 = H$

(154), R^1 =  ; $R^2 = H_2$; $R^3 = R^4 = H$

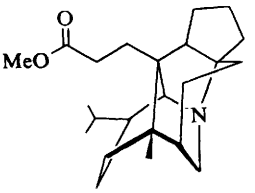
(155), R^1 =  ; $R^2 = O$; $R^3 = H$; $R^4 = OH$



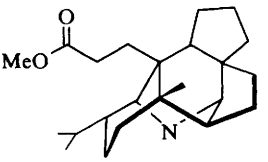
(156)



(157), $R^1 = OAc$; $R^2 = CH_2OAc$; $R^3 = OH$; $R^4 = H$
(158), $R^1 = OAc$; $R^2 = CH_3$; $R^3 = OH$; $R^4 = H$
(159), $R^1 = H$; $R^2 = CH_2OH$; $R^3 = R^4 = H$
(160), $R^1 = OH$; $R^2 = CH_2$; $R^3 = OH$; $R^4 = H$
(161), $R^1 = OAc$; $R^2 = CH_2OAc$; $R^3 = OH$; $R^4 = H$; *N*-oxide
(162), $R^1 = H$; $R^2 = CH_2OAc$; $R^3 = R^4 = H$
(163), $R^1 = H$; $R^2 = CHO$; $R^3 = R^4 = OH$



(164)

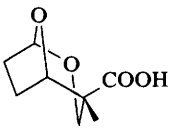


(165)

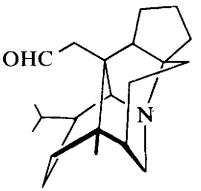
of each group, *i.e.* (152), (154), (155), (156), (157), and (162), were determined by *X*-ray crystallography. The absolute stereochemistry rests on a recent *X*-ray study of daphmacrine methiodide.[88] This proved to be the mirror image of the structures drawn in all other papers on the alkaloids. Since the alkaloids are so closely related, the revised absolute stereochemistry has been adopted for all in this review.

Two other interesting compounds found in the plant were methyl homodaphniphyllate (164) and methyl homosecodaphniphyllate (165).

B. Chemistry.—In the course of structural work[89] the α-ketol derived from daphniphylline (152) was cleaved, using periodate, to the acid (166) and the aldehyde (167).



(166)



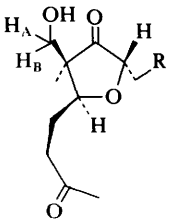
(167)

The latter was converted *via* the alcohol, toluene-*p*-sulphonate, and nitrile to homodaphniphyllic acid. Its methyl ester (164) was subsequently found as a natural product.[90]

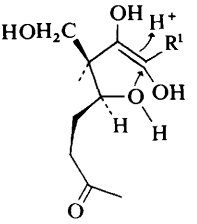
The action of 6N-HCl at 80 °C on daphniphylline (152) or the corresponding alcohol gave desacetyl isodaphniphylline.[89] Isodaphniphylline could be produced by acetylation of the desacetyl derivative or by the action of hot acetic acid on daphniphylline hydrochloride, followed by liberation of the base. Desacetyldaphniphylline had ν_{max} 1753 (five-membered ring ketone) and 1714 cm^{-1}. Its n.m.r. spectrum showed that a methyl ketone was present (δ 2.14). An AB quartet (2H, J = 11 Hz) centred at δ 3.49 was shifted to δ 3.99 in the spectrum of isodaphniphylline. This corresponds to the presence of HO–CH_AH_B–C–. On this basis, structure (168) (R is the heterocyclic ring system) was assigned to isodaphniphylline. The reaction probably involves hydrolytic opening of the ketal, followed by addition of the isolated secondary hydroxy-group to the enediol from the α-ketol [see (169)]. Since the configuration of the centre adjacent to the carbonyl can be equilibrated, and the other asymmetric centres are not disturbed, the configuration of isodaphniphylline is suggested to be as in (168).

Another interesting reaction observed in the series was the oxidation of methyl homosecodaphniphyllate (165).[91] Lead tetra-acetate in benzene converted this

[88] C. S. Gibbons and J. Trotter, *J. Chem. Soc. (B)*, 1969, 840.
[89] H. Irikawa, N. Sakabe, S. Yamamura, and Y. Hirata, *Tetrahedron*, 1968, **24**, 5691.
[90] M. Toda, S. Yamamura, and Y. Hirata, *Tetrahedron Letters*, 1969, 2585.
[91] M. Toda, H. Irikawa, S. Yamamura, and Y. Hirata, *J. Chem. Soc. Japan*, 1970, **91**, 103.

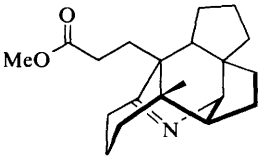


(168)

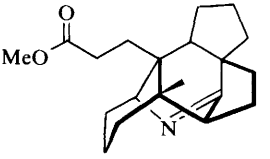


(169)

to a dehydro-compound ($C_{23}H_{35}O_2N$) which could be reduced back to (165) by sodium borohydride. This suggested that the product was an azomethine. Of the two possible azomethines with the original skeleton, (170) and (171), the latter



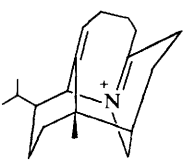
(170)



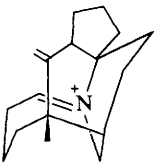
(171)

seems geometrically impossible so the somewhat strained structure (170) was assigned. As would be expected for a distorted azomethine bond, the band attributable to the C=N stretching vibration was at 1589 cm^{-1}—*i.e.* it had much single bond character.

The mass spectra of the daphniphylline[89] group of alkaloids have prominent peaks corresponding to two cleavages. The corresponding ions are postulated to be (172) and (173) or (174) for the case of daphniphylline itself.

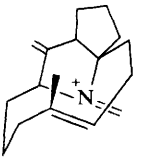


m/e 272
(172)



(173)

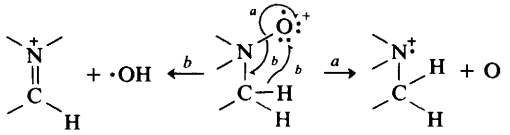
m/e 286



(174)

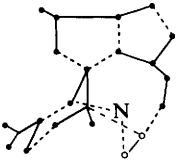
Macrodaphnine loses an atom of oxygen or a hydroxyl radical on electron impact,[92] as illustrated in Scheme 2.

[92] T. Nakano and B. Nilsson, *Tetrahedron Letters*, 1969, 2883.

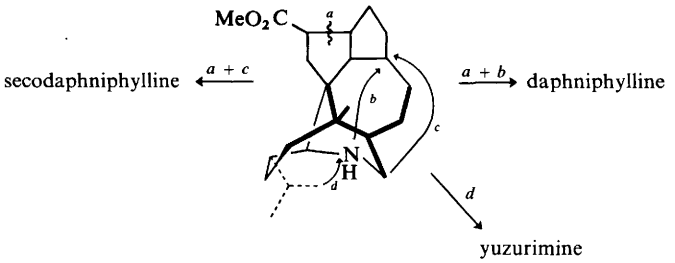


Scheme 2

C. Biogenetic Speculation.—Harata and co-workers[91] discerned a possible origin of the yuzurimine skeleton in two monoterpene units and an acetate unit joined in an unusual way [see (175)]. The intermediate could readily give all three

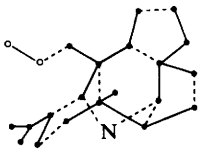


(175)



Scheme 3

skeletons as shown in Scheme 3. However, an equally plausible postulate is that the secodaphniphylline skeleton is the original one, formed from three isoprene units and an acetate unit [see (176)]. No biosynthetic experiments have been reported.



(176)

We thank Professor K. Wiesner for sending manuscripts in advance of publication, and Mr. V. Poppe and Dr. T. Yokata for translations from Russian and Japanese respectively.

17

Steroidal Alkaloids of the Apocynaceae and Buxaceae

BY R. GOUTAREL

Introduction

Since the establishment of the structure of conessine (1), and the discovery of numerous steroidal amines, the theoretical and economic interest of the steroidal amines and alkaloids has stimulated very active chemical research on the plants of the Apocynaceae and Buxaceae families. The main points in this work are set out in two monographs.[1,2] The present account is confined to the results obtained since 1966 and deals only with the Apocynaceae and Buxaceae families. The Solanaceae and *Veratrum* groups are not included.

PART I: Alkaloids of the Apocynaceae

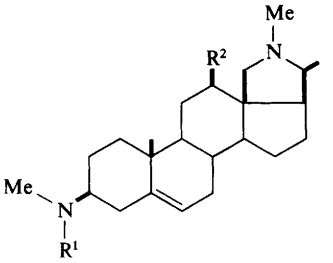
1 The *Holarrhena* and *Paravallaris* Alkaloids

Leaving aside the very important discovery of the amino-glyco-steroids, the study of further plants of the Apocynaceae family has led to the isolation of bases showing only a few modifications in previously established structures.

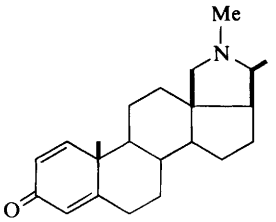
A. Steroidal Alkaloids and Amines.—Conessine (1) is found in the bark of all the *Holarrhena* species which have been studied. It is accompanied by other derivatives of conanine; thus, holarrhenine (2), holarrheline (3), holadienine (4), holaromine (5) (possibly an artefact), and holaline (6)[3] are found in *H. floribunda*.[4]

Conkurchine (7) has been extracted from the leaves and bark of *H. crassifolia*.[5] Conessine, the nor-conessines, and holadienine have been isolated from the bark of *H. mitis*.[6] Holarrhimine (8) and methylholarrhimine II (9) have also been isolated in fairly large quantity from the same plant.

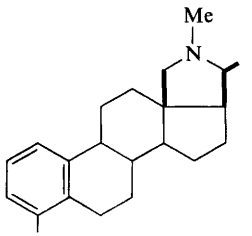
[1] R. Goutarel, 'Les Alcaloïdes stéroïdiques des Apocynacées,' Hermann, Paris, 1964.
[2] R. H. F. Manske, 'The Alkaloids,' Academic Press, New York, London, 1967, vol. IX; V. Černy and F. Šorm, 'Alkaloids of Apocynaceae and Buxaceae,' p. 305.
[3] M.-M. Janot, Ph. Devissaguet, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 4315.
[4] M.-M. Janot, Ph. Devissaguet, Q. Khuong-Huu, and R. Goutarel, *Ann. pharm. franç.*, 1967, **25**, 733.
[5] Q. Khuong-Huu, J. Einhorn, C. Monneret, and R. Goutarel, unpublished work.
[6] G. P. Wannigama, A. Cavé, and R. Goutarel, unpublished work.



(1), R^1 = Me, R^2 = H
(2), R^1 = Me, R^2 = OH
(3), R^1 = H, R^2 = OH



(4)



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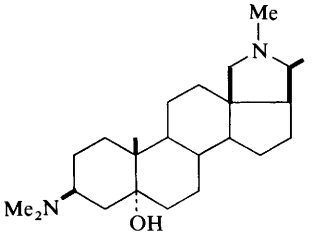
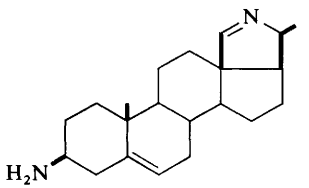


(6)



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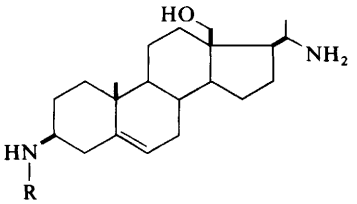
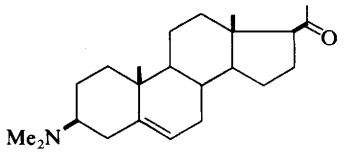
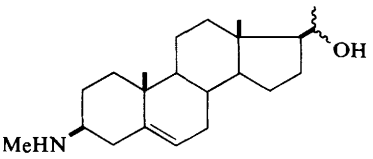


(8), R = H
(9), R = Me

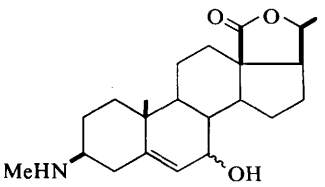


(10)

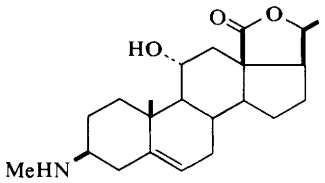


(11), 20α-OH
(12), 20β-OH

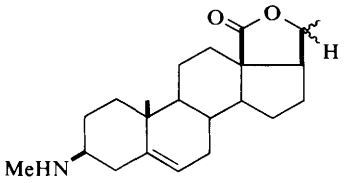
Leaves of the various *Holarrhena* species contain steroidal amines characteristic of the species. Thus, methylholaphylline (10), holaphyllinol (11), holaphyllidine (12), and dihydroholaphyllamine (3β-amino-20-oxo-5α-pregnane) are found in the leaves of *H. floribunda*.[7]



(13), 7α-OH
(14), 7β-OH



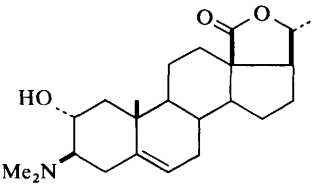
(15)



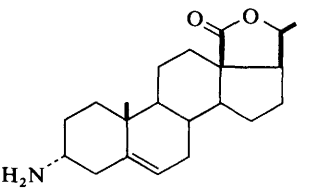
(16), 20*S*
(17), 20*R*

7α-Hydroxyparavallarine (13), 7β-hydroxyparavallarine (14), and 11α-hydroxyparavallarine (15) have been extracted from *Paravallaris microphylla*.[8,9] Paravallarine (16), 20-epi-paravallarine (17), 2α-hydroxy-*N*-methyl-20-epi-paravallarine (18),[10] and gitingensine (19) (*cf.* kibataline[2]) have been found in *Kibatalia gitingensis*.[11]

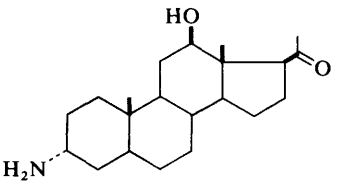
[7] M. LeBœuf, A. Cavé, and R. Goutarel, *Ann. pharm. franç.*, 1969, **27**, 217.
[8] L. Fernandés, H.-P. Husson, P. Potier, and J. Le Men, *Compt. rend.*, 1967, **264**, *C*, 2165.
[9] H.-P. Husson, L. Fernandés, P. Potier, and J. Le Men, *Bull. Soc. chim. France*, 1969, 3162.
[10] A. Cavé, P. Potier, and J. Le Men, *Ann. pharm. franç.*, 1967, **25**, 107.
[11] G. Aguilar-Santos, E. Santos, and P. Crabbé, *J. Org. Chem.*, 1967, **32**, 2642.



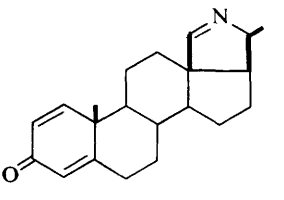
(18)



(19)



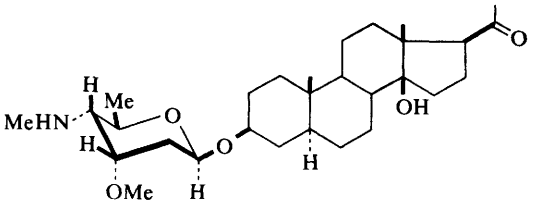
(20)



(21)

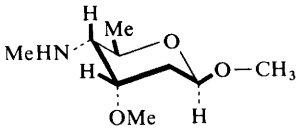
Bokitamine (20) (12β-hydroxyfuntumine) has been isolated from the leaves of an African *Holarrhena* species, *H. wulfsbergii*.[12] Maingayine (21), from *Paravallaris maingayi*,[13] combines the characteristics of both conkurchine (7) and holadienine (4).

B. Amino-glyco-steroids.—The term amino-glyco-steroid is used to denote a new class of glyco-alkaloids where an amino-sugar is linked to a steroidal genin. When such compounds contain a cardenolide as genin, they are known as amino-glyco-cardenolides. Amino-glyco-steroids have been isolated, so far, from the leaves of only Asiatic *Holarrhena* species. The first amino-glyco-steroid, holacurtine (22), was extracted from the leaves of *H. curtisii*.[14] Methanolysis of (22) with hydrogen chloride gave a genin, holadiolone, 3β,14β-dihydroxy-5α-pregnan-20-one, and an amino-sugar, *N*-methyl-D-holosamine (4-deoxy-4-methylamino-D-cymarose), isolated as the β-methylglycoside (23). Holacurtine is 3β-(4′-methylamino-3′-*O*-methyl-2′,4′,6′-trideoxy-β-D-ribohexopyranosyl)-14β-hydroxy-5α-pregnan-20-one.

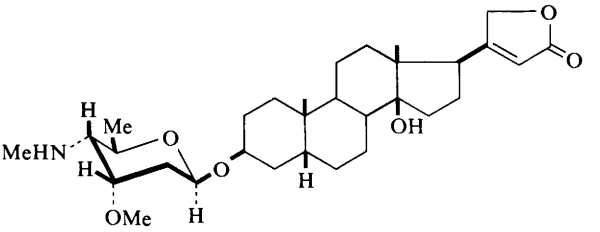


(22), holacurtine

[12] S. Nellé, G. Charles, A. Cavé, and R. Goutarel, *Compt. rend.*, 1970, **271**, *C*, 153.
[13] J. B. Davis, K. Jewers, A. H. Manchanda, and A. B. Wood, *Chem. and Ind.*, 1970, 627.
[14] M.-M. Janot, Ph. Devissaguet, Q. Khuong-Huu, J. Parello, N. G. Bisset, and R. Goutarel, *Compt. rend.*, 1968, **266**, *C*, 388.



(23)



(24), mitiphylline

The structure of the amino-sugar was shown by n.m.r. (double resonance) methods and confirmed by synthesis from the α-methylglycoside of D-cymarose (introduction of an amino-group at C-4 through an azide, itself obtained by double inversion of the 4-hydroxy-group[15]).

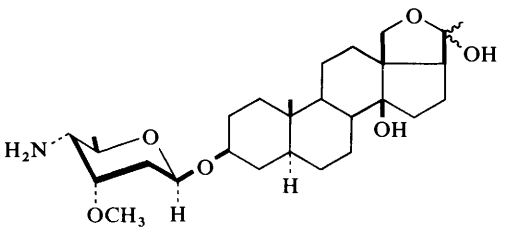
It should be noted that *H. crassifolia*, from Cambodia and Laos, though stated to be identical with the Malaysian *H. curtisii*, does not contain any amino-glycosteroids. Conkurchine (7) is the major alkaloid isolated from the leaves of this species.[5]

Mitiphylline (24), the first amino-glyco-cardenolide, was isolated from the leaves of *H. mitis*, an Apocynacea from Ceylon.[16] On methanolysis with hydrogen chloride, mitiphylline gave (23) and digitoxigenin.

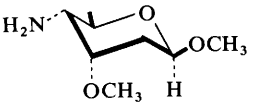
Holantosine-A (25) and holantosine-B (26) have been isolated from the leaves of a *Holarrhena antidysenterica*[17] from India. Their two genins, holantogenin and anhydro-holantogenin respectively, are interconvertible. Holantogenin gives anhydro-holantogenin on dehydration (sublimation under high vacuum), while anhydro-holantogenin gives holantogenin on addition of water (aqueous ethanol or dioxan). These genins are of the same type as stapelogenin (28)[18] and adonilide (29).[19]

The holantosines -A and -B give the β-methylglycoside of D-holosamine (27) on treatment with hydrogen chloride in methanol. The synthesis of this methylglycoside has been effected.[15,17] The structure of holantosine-B was established by n.m.r. at 220 MHz.

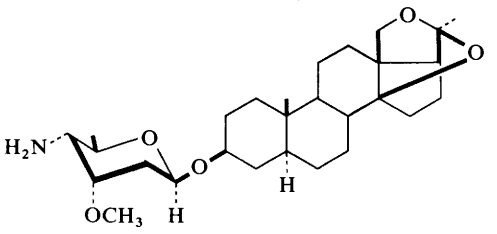
[15] J. Hildesheim, S. D. Géro, Q. Khuong-Huu, and C. Monneret, *Tetrahedron Letters*, 1969, 2849.
[16] M.-M. Janot, M. Lebœuf, A. Cavé, R. Wijesekera, and R. Goutarel, *Compt. rend.*, 1968, **267**, *C*, 1050.
[17] M.-M. Janot, Q. Khuong-Huu, C. Monneret, I. Kaboré, J. Hildesheim, S. D. Géro, and R. Goutarel, *Tetrahedron*, 1970, **26**, 1695.
[18] U. Eppenberger, W. Vetter, and T. Reichstein, *Helv. Chim. Acta*, 1966, **49**, 1505.
[19] Y. Shimizu, Y. Sato, and H. Mitsuhashi, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 2005.



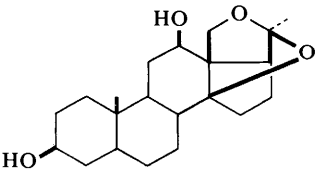
(25), holantosine-A



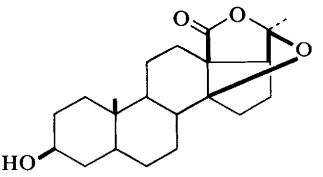
(27)



(26), holantosine-B

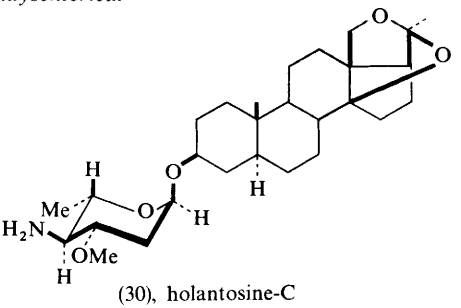


(28)



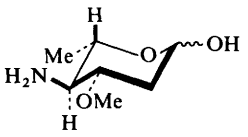
(29)

Holantosine-C (30), the α-L-glycoside of anhydro-holantogenin and of a new amino-sugar, L-holantosamine, 4-amino-4-deoxy-L-oleandrose, has been isolated from Indian *H. antidysenterica*.[20]

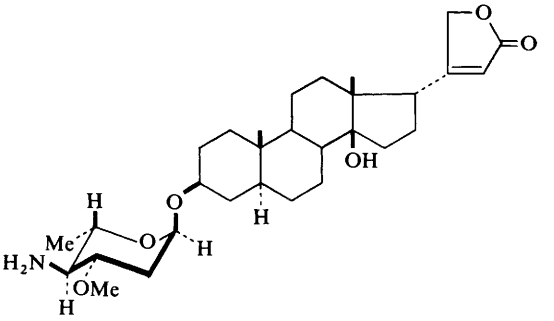


(30), holantosine-C

[20] Q. Khuong-Huu, C. Monneret, P. Choay, J. M. Tekam, I. Kaboré, and R. Goutarel, *Bull. Soc. chim. France*, in the press.



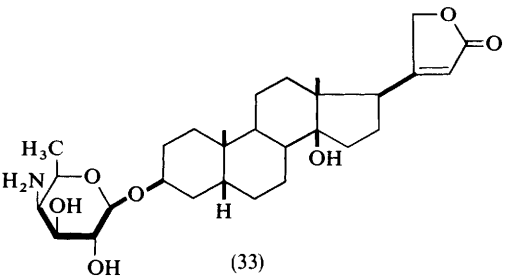
(31)



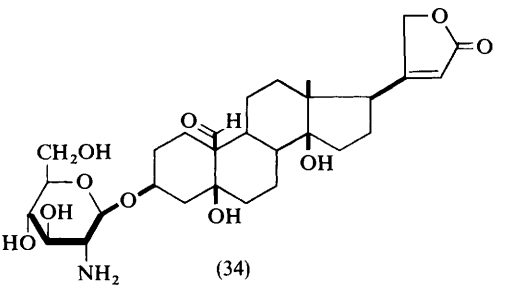
(32), holarosine-A

A new amino-glyco-cardenolide, holarosine-A (32), was isolated from the leaves of a *Holarrhena antidysenterica* from Viet-Nam. Methanolysis of this compound gave the α-L-methylglycoside of L-holantosamine (31) and allo-uzarigenin.[20]

Interest in the possible cytotoxic activity of the amino-glyco-cardenolides has led to the synthesis of 3β-(4'-amino-4',6'-dideoxy-β-D-galactopyranosyl)-14β-hydroxy-5β-card-20(22)-enolide (33)[21] and the 2-amino-2-deoxy-β-D-gluco-pyranosides of digitoxigenin, of strophanthidine (34), and of pregnenolone.[22]



(33)



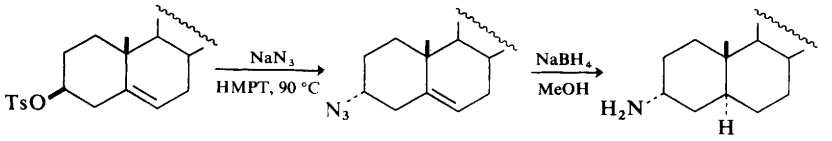
(34)

[21] C. L. Stevens, G. H. Ransford, and G. E. Cutowski, 156th ACS National Meeting, Abstract of Papers, IX, 1968, MEDI 9.

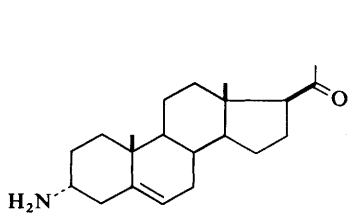
[22] W. Meyer zu Reckendorf, N. Wassiliadou-Michaeli, and H. Machleidt, *Arch. Pharm.*, 1970, **303**, 17.

2 Synthesis of Amino-steroids

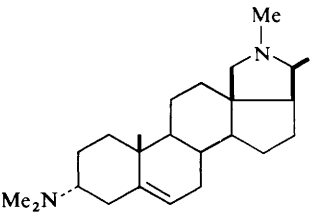
The stereospecific introduction of an amino-group at C-3 in a Δ^5-steroid can be effected by reduction of the corresponding azide. The 3α-azido-Δ^5-steroids are obtained with inversion of configuration when the corresponding 3β-tosyloxy-Δ^5-steroids are treated with sodium azide in an aprotic dipolar solvent.[23] The 3α-azido-Δ^5-steroids can be obtained in yields of 90% when hexamethylphosphotriamide (HMPT) is used as solvent. The reduction of the 3α-azido-group can be effected with $LiAlH_4$–ether, or with Raney nickel–hydrazine hydrate[25] in cases where the steroid contains other groups reducible by $LiAlH_4$.[24] While azides in general are not reduced by borohydrides of the alkali metals, 3α-azido-Δ^5-steroids are reduced to the saturated 3α-amino-5α-steroids (Scheme 1).[26] Holamine (35) and conkuressine (36)[23] were obtained by this method.



Scheme 1



(35)

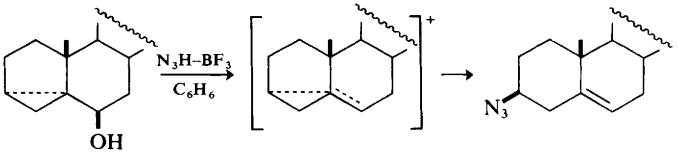


(36)

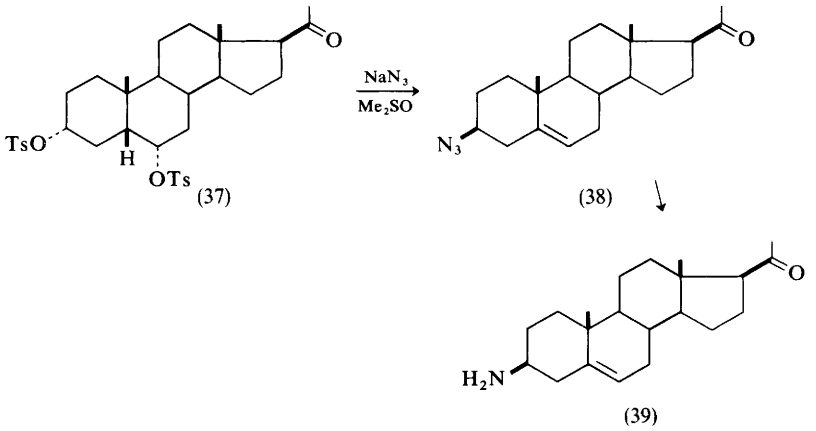
The 3β-azido-Δ^5-steroids are obtained on treatment of the 3β-tosyloxy-Δ^5-steroids, or better the 3α,5α-cyclo-6-hydroxy-steroids, with a solution of hydrazoic acid in benzene in the presence of an excess of BF_3.[27] Reduction of the azide function is effected with $LiAlH_4$ (Scheme 2). Holaphyllamine (39) has been prepared from 3α,6α-ditosyloxy-5β-pregnan-20-one (37), by way of the azide (38).[28]

The introduction of a 20α-amino-group in a steroid can be effected starting from the corresponding acid and making use of the stereospecificity of the

[23] A. Cavé, F. X. Jarreau, Q. Khuong-Huu, M. Lebœuf, N. Serban, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 701.
[24] R. Goutarel, C. Conreur, L. Djakouré, M. Lebœuf, and A. Cavé, *Tetrahedron*, 1968, **24**, 7013.
[25] K. Ponsold, *Chem. Ber.*, 1963, **96**, 1411.
[26] O. E. Edwards, A. Cavé, and R. Goutarel, unpublished work.
[27] F. X. Jarreau, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1963, 1861.
[28] F. Hodosan and N. Serban, *Experientia*, 1968, **24**, 881.



Scheme 2

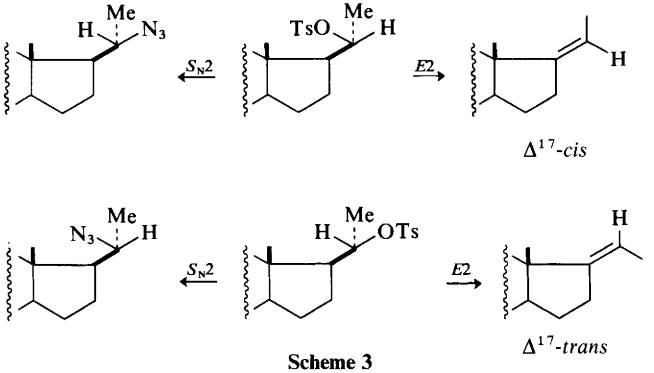


Curtius reaction.[29,30] However, it is sometimes advantageous to use as starting material a steroid containing an oxygen function at C-20. Reduction of steroidal 20-oximes gives a mixture of the epimeric 20α- and 20β-amines. In the case of the oxime of pregnenolone, these two epimers are obtained in equivalent proportions, and it is possible to separate them by chromatography on alumina.[31,32]

On treatment with sodium azide in HMPT, the 20-tosyloxy-steroids give the corresponding 20-azido-derivatives in yields of 60%, with inversion of configuration.[33,34] It has been shown that substitution is of the S_N2 type, and that this reaction is accompanied by an *E*2 type of elimination reaction leading to one other product. Thus, the 20β-tosyloxy-steroids give 20α-azido-steroids and Δ^{17}-*cis*-derivatives, while the 20α-tosyloxy-steroids give 20β-azido-steroids and Δ^{17}-*trans*-derivatives, as in Scheme 3.

Replacement of sodium azide by other nucleophiles (formates, acetates, benzoates, or cyanates) gives the elimination derivative as the major reaction

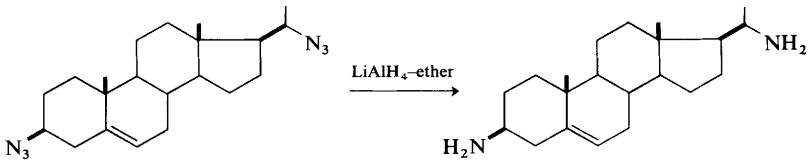
[29] P. L. Julian, E. W. Meyer, and R. C. Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 887.
[30] V. Černy, L. Labler, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1957, **22**, 76.
[31] R. Goutarel, H. R. Mahler, G. Green, Q. Khuong-Huu, A. Cavé, C. Conreur, F. X. Jarreau, and J. Hannart, *Bull. Soc. chim. France*, 1967, 4575.
[32] G. van de Woude and L. van Hove, *Bull. Soc. chim. belges*, 1967, **76**, 566.
[33] M. Lebœuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 2100.
[34] M. Lebœuf, A. Cavé, and R. Goutarel, *Compt. rend.*, 1967, **264**, *C*, 1090.



Scheme 3

product in HMPT.[35,36] The stereospecificity of substitution of tosylate by azide in HMPT has made it possible to prepare 17aα-amino-D-homoandrostanes in good yield.[37] The 20α- or 20β-configuration of the azido- and amino-steroids is easily determined by n.m.r.[38] or by circular dichroism.[39]

The four 3,20-diaminopregn-5-enes have been obtained from pregnenolone by means of stereospecific methods for the introduction of amino-functions at C-3 and C-20. Irehdiamine -A(41) is obtained by reduction ($LiAlH_4$) of 3β,20α-diazidopregn-5-ene (40).[31]



(40) (41)

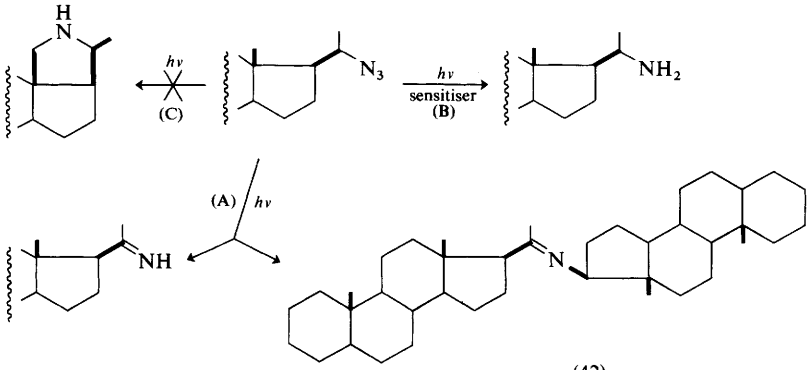
The same methods have been used in the synthesis of the alkaloids of *Sarcococca pruniformis*, which are derivatives of 3α,20α-diaminopregn-5-ene and 3α,20α-diamino-5α-pregnane.[24]

3 Photochemistry of the Azido-steroids

Although a synthesis of conessine from 3β,20α-diazidopregn-5-ene (40) has been described earlier,[40] its validity has been questioned.[41] A re-examination of the

[35] M. Lebœuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1969, 1619.
[36] M. Lebœuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1969, 1624.
[37] M. Lebœuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1969, 2100.
[38] C. H. Robinson and P. Hofer, *Chem. and Ind.*, 1966, 377.
[39] D. Bertin and M. Legrand, *Compt. rend.*, 1963, **256**, 960.
[40] D. H. R. Barton and L. R. Morgan jun., *J. Chem. Soc.*, 1962, 624.
[41] D. H. R. Barton and A. N. Staratt, *J. Chem. Soc.*, 1965, 2444.

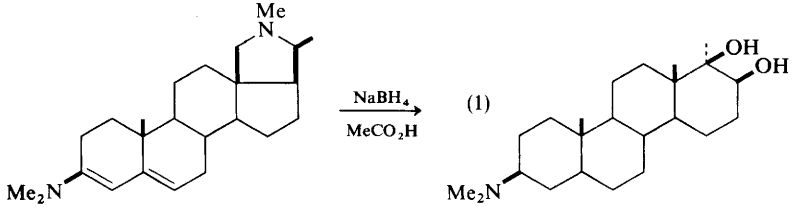
synthetic route was undertaken, particularly since steroids with azido-groups at C-3 and C-20 are easy to prepare. Photolysis of (40) in cyclohexane gives a mixture of 3,20-bis(dimethylamino)pregn-5-enes, after reduction of the crude reaction product and methylation. No trace of conessine could be detected, and polymerisation products were seen to be formed. The reaction has been studied on the mono-azido-derivative, 20α-azido-5α-pregnane.[42,43] Three reaction paths have earlier[40] been postulated for this reaction: (A) isomerisation to an imine; (B) formation of a primary amine by abstraction of hydrogen from the solvent; (C) 1,5-abstraction of hydrogen followed by cyclisation to a pyrrolidine. Only path (A) is observed in every case. Path (B) is observed only in the presence of a sensitiser, and path (C) is excluded.



(42)

The major product of the reaction is the bis-steroidal Schiff base (42), formed after dimerisation of the nitrene intermediate.

The total synthesis of conessine by Marshall and Johnson[44,1,2] is treated further in a general article on the total synthesis of steroids.[45] The 3β-dimethylamino-group is introduced by reduction ($NaBH_4$–acetic acid) of the dienamine (43) obtained from Δ^4-conanen-3-one. It is by this method, followed by catalytic



(43) (44)

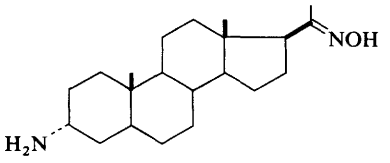
[42] Q. Khuong-Huu and A. Pancrazi, *Tetrahedron Letters*, 1968, 4221.
[43] A. Pancrazi, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1970, 4446.
[44] J. A. Marshall and W. S. Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 1485.
[45] W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron*, 1966, suppl. 8, part II, 541.

reduction, that the 3β-dimethylamino-group has been introduced in the synthesis of dictyolucidamine (44) from 17α-hydroxyprogesterone.[46]

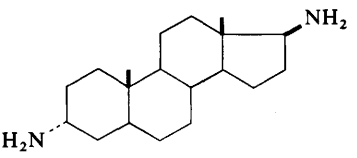
4 Reactions and Transformations of the Steroidal Amines and Alkaloids

The steroidal amines and alkaloids are starting materials for the preparation of steroids used in therapy, and are excellent substrates for the study of many reactions.

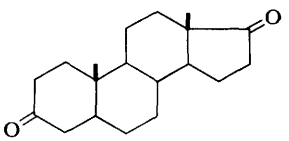
Steroidal amines with nitrogen at C-3 or C-20 can be converted into steroidal hormones.[47] Beckmann rearrangement of the oxime (45) of funtumine gives 3α,17β-diamino-5α-androstane (46). Ruschig deamination of the latter[48] gives androstanedione (47).[47,49] In the same way, the alkaloids of *H. floribunda*, holaphylline, holaphyllamine, and holamine (48) give the 3,17-diaminoandrost-5-enes [(48 gives (49)] which are deaminated to androst-4-ene-3,17-dione.[50]



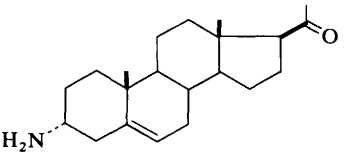
(45)



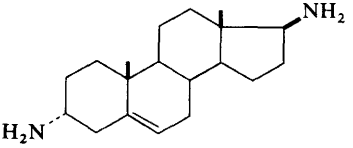
(46)



(47)



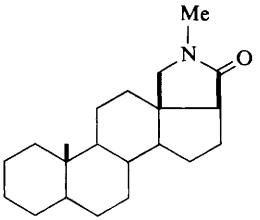
(48)



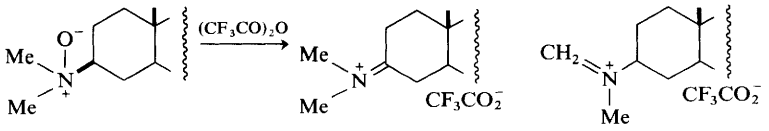
(49)

[46] M.-M. Janot, C. Monneret, X. Monseur, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1966, 3472.
[47] R. Goutarel, *Bull. Soc. chim. France*, 1964, 1665.
[48] H. Ruschig, W. Fritsch, J. Schmidt-Thomé, and W. Haede, *Chem. Ber.*, 1955, **88**, 883.
[49] L. I. Stekolnikov, *Priroda*, 1969, 108 (*Chem. Abs.*, 1970, **72**, 435).
[50] M. Lebœuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1965, 1697.

The oxidation of steroidal 3α-, 3β-, 20α-, and 20β-amines with *m*-chloroperbenzoic acid to the corresponding nitro-compounds has been described.[51] Oxidation of several steroidal tertiary amines with chromic acid in pyridine leads to the corresponding *N*-formyl derivatives.[52] Photosensitised irradiation (methylene blue) of 20α- and 3β-dimethylamino-steroids leads to a secondary amine in 80% yield. The formyl derivative (10% yield) is not an intermediate in the *N*-demethylation reaction. 3α-Dimethylamino-5α-pregnane gives 5α-pregnan-3-one and the secondary amine. Conanine gives the lactam (50).[53]



(50)



(51) (52) (53)

The reaction of trifluoroacetic anhydride on the *N*-oxides of 3β-dimethylamino-steroids (51) (*e.g.*, *N*-methyl-5α-dihydroparavallarine) leads to the immonium salts (52) and (53), which can be hydrolysed to the 3-keto- or the 3-methylamino-steroid, respectively.[54] This reaction is generally applicable to other amines: trimethylamine oxide is converted into *NN*-dimethylformaldimmonium trifluoroacetate (54), which is an excellent Mannich reagent.[55]

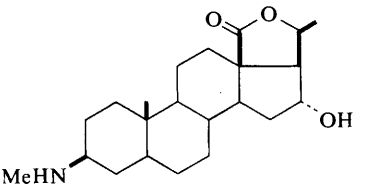
$$H_2C{=}\overset{+}{N}(CH_3)_2,\quad CF_3CO_2^-$$

(54)

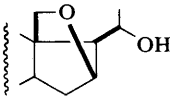
$LiAlH_4$ reduction of the tosyl ester of dihydroparavallaridine (55) gives 16β,18-oxido-derivatives (56).[56] The corresponding 17β-dimethylamino-derivative has

[51] C. H. Robinson, L. Milewich, and P. Hofer, *J. Org. Chem.*, 1966, **31**, 524.
[52] A. Cavé, C. Kan-Fan, P. Potier, J. Le Men, and M.-M. Janot, *Tetrahedron*, 1967, **23**, 4691.
[53] D. Herlem and F. Khuong-Huu, *Compt. rend.*, 1969, **269**, *C*, 1405.
[54] A. Cavé, C. Kan-Fan, P. Potier, and J. Le Men, *Tetrahedron*, 1967, **23**, 4681.
[55] A. Ahond, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan, and P. Potier, *J. Amer. Chem. Soc.*, 1968, **90**, 5622.
[56] H.-P. Husson, P. Potier, and J. Le Men, *Bull. Soc. chim. France*, 1966, 2256.

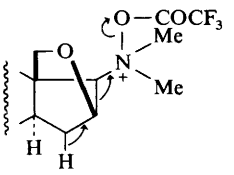
been prepared. Its *N*-oxide (57) undergoes an interesting fragmentation reaction[55,57] when treated with trifluoroacetic anhydride to give the aldehyde (58).



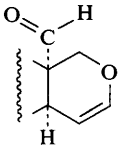
(55)



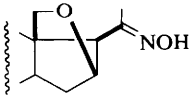
(56)



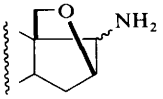
(57)



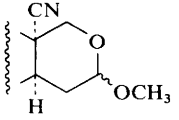
(58)



(59)



(60)



(61)

Beckmann rearrangement of the oxime (59), prepared from (56), gives the two amines (60). Ruschig degradation[48] (treatment of the *N*-chloro-derivative with NaOMe)[57] gives the nitriles (61).

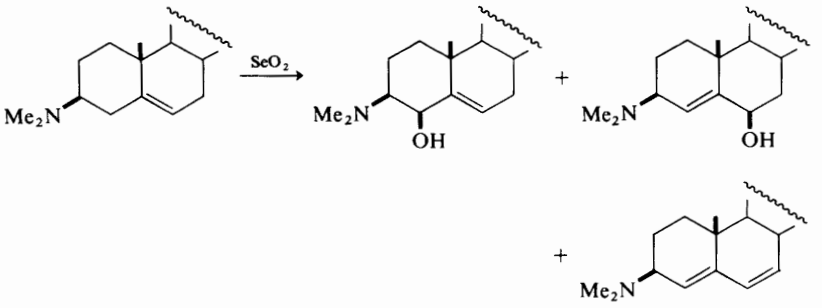
Selenium dioxide oxidation of the 3α and 3β-dimethylamino-Δ^5-steroids of the paravallarine series gives not only the 4β-hydroxy-derivative, but also the 6β-hydroxy-Δ^4-steroid and the 4,6-diene, as shown in Scheme 4.[58]

16β-Amino-3β-dimethylamino-18,20(*R*)-oxido-5α-pregnane (62) has been prepared from paravallaridine. An intramolecular transfer of a hydride ion from C-20 has been observed during the methylation (HCO_2H–HCHO) of (62) to (63).[59]

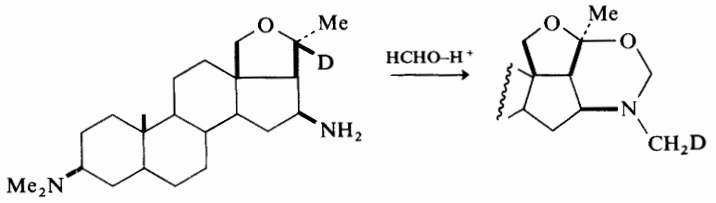
[57] H.-P. Husson, J. de Rostolan, Y. Pépin, P. Potier, and J. Le Men, *Tetrahedron*, 1970, **26**, 147.

[58] H.-P. Husson, L. Fernandès, P. Forgacs, R. Tiberghien, P. Potier, and J. Le Men, *Bull. Soc. chim. France*, 1969, 1993.

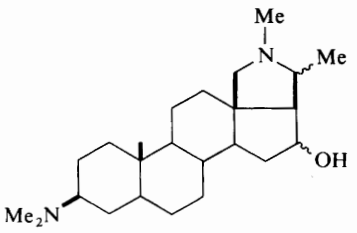
[59] H.-P. Husson, J. de Rostolan, P. Potier, and J. Le Men, *Bull. Soc. chim. France*, 1966, 3379.



Scheme 4



(62) (63)



(64)

The alcohols epimeric at C-16 in the dihydroconessine series and in the dihydroheteroconessine series (64) have been prepared from paravallaridine.[60]

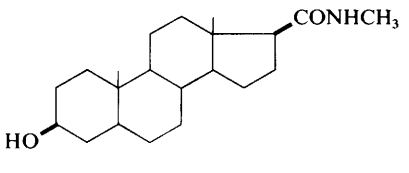
Nitrous acid deamination (aqueous acetic acid) of 3β-amino-5α-cholestane gives mainly substitution derivatives with retention of configuration. The reaction is, however, accompanied by elimination. 3α-Amino-cholestane gives the 3α-derivative, along with large amounts of elimination products.[61] 20α-Amino-5α-pregnanes give substitution derivatives (especially alcohols) with

[60] H.-P. Husson, R. Beugelmans, P. Potier, and J. Le Men, *Bull. Soc. chim. France*, 1966, 2516.

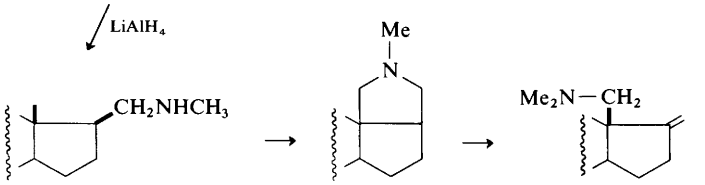
[61] C. W. Shoppee, R. E. Lack, and P. Ram, *J. Chem. Soc. (C)*, 1966, 1018.

retention of configuration, while 20β-amino-5α-pregnanes give exclusively rearrangement products of the D-homoandrostane series.[62]

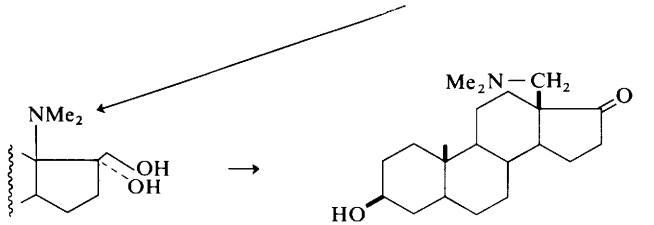
18-Dimethylamino-3β-hydroxyandrostan-17-ones (70), epimeric at C-5, were prepared from methylamides of the corresponding 3β-hydroxyetianic acids:



(65)



(66) (67) (68)



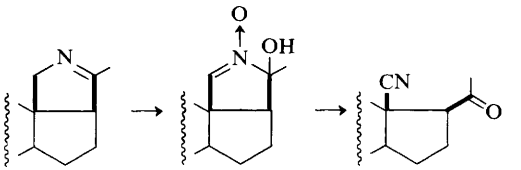
(69) (70)

The amide (65) was reduced by $LiAlH_4$ to give (66), which was cyclised using the Loeffler–Freytag reaction to give (67). The latter was subjected to a Hofmann degradation to give (68), which was then oxidised to the amino-ketone (70).[63]

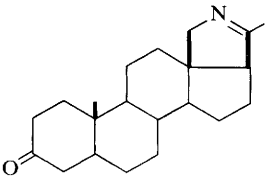
The alkaloids holarrhimine (6), paravallarine (16), and conessine (1) are steroids substituted at C-18, and the possibility of their conversion into steroids of the aldosterone group has been described.[1,2] Conessine, which occurs widely, is an excellent starting material. The sequence described earlier,[1,2] *i.e.*

[62] L. Djakouré, A. Cavé, and R. Goutarel, *Compt. rend.*, 1970, **270**, *C*, 744.
[63] J. Hora and F. Šorm, *Coll. Czech. Chem. Comm.*, 1968, **33**, 2059.

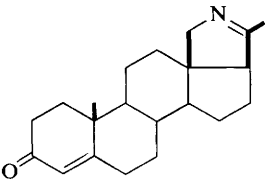
(71) → (72) → (73), was used in the synthesis of 18-hydroxy-4,5-dihydroprogesterone[64] and 18-hydroxyprogesterone[65] from the imines (74) and (75), respectively, which were in turn prepared from conessine.[66—68]



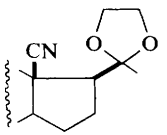
(71) (72) (73)



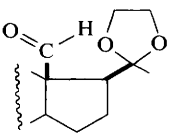
(74)



(75)



(76)

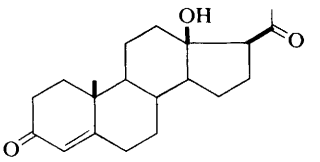


(77)

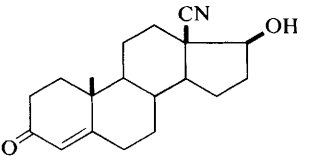
Reduction of the dioxolan-nitrile (76) by $LiAlH_4$ (ether–N_2) gives the aldehyde (77), which is reduced to the 18-hydroxy-steroid ($NaBH_4$) and hydrolysed (aqueous AcOH) to the 18-hydroxy-20-keto-steroid in the hemiacetal form.

Treatment of the nitrile (76) in tetrahydrofuran with $LiAlH_4$ in the presence of air leads to substitution of the nitrile group by hydroxyl with retention of configuration.[69] 18-Nor-13β-hydroxyprogesterone (78) was obtained in this manner.[65]

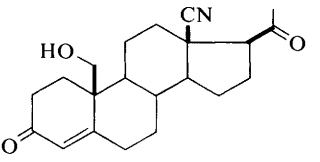
[64] M.-M. Janot, X. Lusinchi, L. Labler, and R. Goutarel, *Bull. Soc. chim. France*, 1966, 3276.
[65] M. Lebœuf, A. Cavé, C. Conreur, X. Lusinchi, and R. Goutarel, *Ann. pharm. franç.*, 1969, **27**, 289.
[66] H. A. Kasal, V. Černy, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2849.
[67] F. Buzetti, W. Wicki, J. Kalvoda, and O. Jeger, *Helv. Chim. Acta*, 1959, **42**, 388.
[68] J. Hora, V. Černy, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2731.
[69] S. Julia, L. Linarès, and P. Simon, *Bull. Soc. chim. France*, 1963, 2471.



(78)



(79)

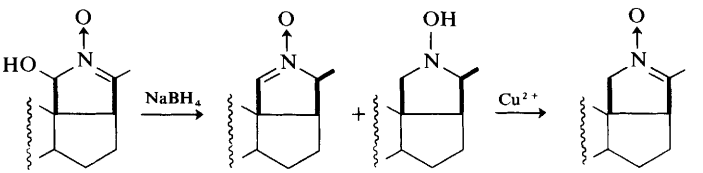


(80)

18-Nitrilo-testosterone (79) was prepared by Baeyer–Villiger degradation of the side-chain of 18-nitrilo-5α-pregnane-3,20-dione, followed by introduction of the Δ^4 double-bond by the usual techniques.[70,71]

Certain derivatives of 18-homoconessine and 18-homolatifoline have been prepared from 18-nitriloprogesterone.[72]

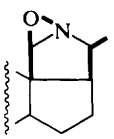
The combination of the degradation of the heterocycle of conanine with the radical cyclisation methods[73—75] for functionalising the 10-methyl group (C-19) has led to the synthesis of 18-nitrilo-19-hydroxyprogesterone (80).[76,77]



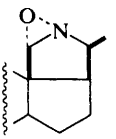
(81) (82) (83) (84)

[70] M.-M. Janot, P. Milliet, X. Lusinchi, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 4310.
[71] M.-M. Janot, P. Milliet, X. Lusinchi, and R. Goutarel, *Compt. rend.*, 1966, **263**, *C*, 785.
[72] J. Kalvoda and G. Anner, *Helv. Chim. Acta*, 1969, **52**, 2106.
[73] K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.
[74] H. Ueberwasser, K. Heusler, J. Kalvoda, C. H. Meyster, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 344.
[75] J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 1361.
[76] X. Lusinchi and G. Roblot, *Bull. Soc. chim. France*, 1967, 3498.
[77] G. Roblot and X. Lusinchi, *Compt. rend.*, 1968, **267**, *C*, 159.

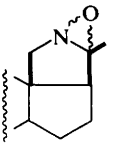
The α-hydroxy-nitrone (72) is isomerised (toluene-*p*-sulphonic acid–benzene) to (81). Reduction of (81) with $NaBH_4$ gives the hydroxylamine (83). Incomplete reduction leads to the nitrone (82). Oxidation of (83) with Cu^{2+} gives the isomeric nitrone (84).[78] The photochemistry of the nitrones (82) and (84) as well as that of the steroidal oxazirans has been studied.[79] Nitrone (82) gives the two oxazirans (85) and (86), while (84) gives a mixture of the oxazirans (87). Irradiation of the oxazirans (87) leads to an azetidine (88, R = Ac).



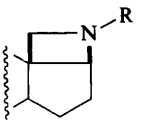
(85)



(86)

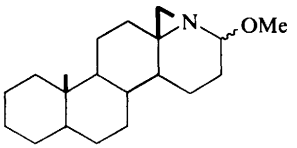


(87)

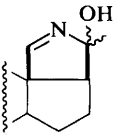


(88) R = H
(89) R = Cl

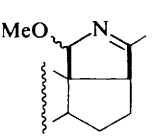
The azetidine (88, R = H), chlorinated to (89, R = Cl) and treated with NaOMe–MeOH, leads to an 18(*N*)-cyclo-17a-aza-D-homoandrostane (90).[80]



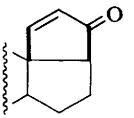
(90)



(91)



(92)



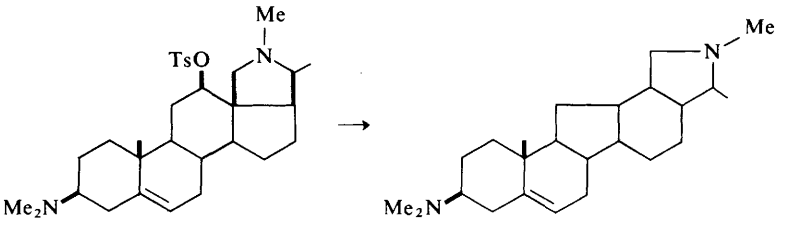
(93)

On treatment in alkaline medium (KOH–EtOH), the α-oxaziran (87) gives (91), which is converted into the conjugated ketone (93) by boiling (KOH–EtOH–H_2O). Refluxing in methanol converts (91) into (92), which has been used to prepare a series of steroids substituted at C-18 and C-20.[81] The circular dichroism of the nitrone chromophores of (82) and (84)[82] and the tertiary amine chromophore of conanine[83] has been studied.

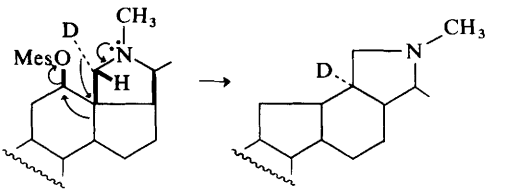
The toluene-*p*-sulphonic ester of holarrhenine (94) gives the rearranged product (95)[84] with $LiAlH_4$–Et_2O. This reaction has been studied in the case of 12β-hydroxyconanine. The sulphonic esters of 12β-hydroxy-5α-conanine (96), on treatment with $LiAlH_4$ or $AlHCl_2$, undergo rearrangement and reduction giving C-nor-D-homoconanine (97). In the presence of deuteriated reagents, C-nor-D-homo-conanine incorporates one atom of deuterium at 18α. This

[78] X. Lusinchi, *Tetrahedron Letters*, 1967, 177.
[79] J. Parello, R. Beugelmans, P. Milliet, and X. Lusinchi, *Tetrahedron Letters*, 1968, 5087.
[80] C. Benezra and X. Lusinchi, *Canad. J. Chem.*, 1969, **47**, 1547.
[81] X. Lusinchi and P. Milliet, *Compt. rend.*, 1967, **265**, *C*, 932.
[82] J. Parello and X. Lusinchi, *Tetrahedron*, 1968, **24**, 6747.
[83] J. Parello and F. Picot, *Tetrahedron Letters*, 1968, 5083.
[84] A. Uffer, *Helv. Chim. Acta*, 1956, **39**, 1834.

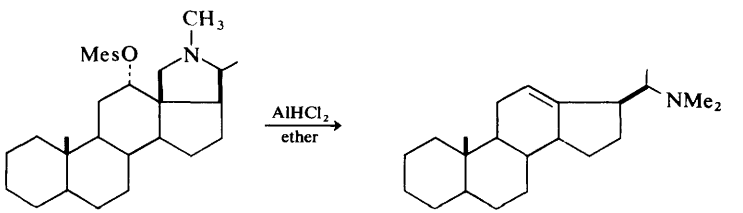
result can be interpreted as a C-nor-D-homo rearrangement accompanied by a hydride shift from C-18 to C-13 leading to an immonium 18(*N*), which is then stereospecifically reduced. This hypothesis is confirmed by carrying out the reaction on 12β-hydroxyconanine containing a deuterium atom at 18α.[85]



(94) (95)



(96) (97)



(98) (99)

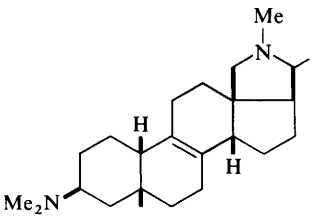
The mesylate of 12α-hydroxyconanine (98) undergoes a Grob fragmentation[86] when treated with $AlHCl_2$–ether, giving (99).[87] The mechanisms of these reactions have been studied using suitably deuteriated derivatives.

[85] G. Lukacs, P. Longevialle, and X. Lusinchi, *Tetrahedron*, 1970, **26**, 583.
[86] C. A. Grob, *Angew. Chem. Internat. Edn.*, 1969, **8**, 535.
[87] G. Lukacs, L. Cloarec, and X. Lusinchi, *Tetrahedron Letters*, 1970, 89.

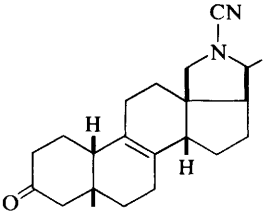
5 Acid-catalysed Rearrangement of Amino-steroids

Siddiqui has described two isomerisation products of conessine in acid medium: isoconessine, obtained by treatment with pure cold sulphuric acid[88] and neoconessine, obtained by treatment with a mixture of sulphuric and acetic acids.[89]

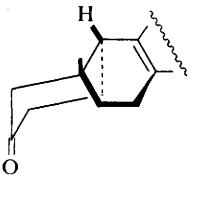
The planar structure of isoconessine (100)[90] has been described.[2] The 5β-methyl stereochemistry of (100) was established by its preparation from a product of the Westphalen rearrangement, alloconessine[91] giving isoconessine in sulphuric acid. The stereochemistry at C-10 is deduced from a study of the circular dichroism of *N*-cyano-*N*-demethylisoconenone (101). This compound gives a positive curve, in agreement with an A–B *cis*-conformation, with ring B as a half-chair, the methyl group at C-5 being axial with respect to the ring B, as in (102).[92]



(100)

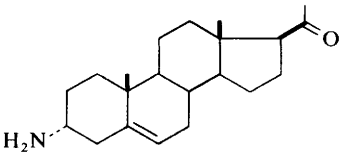


(101)

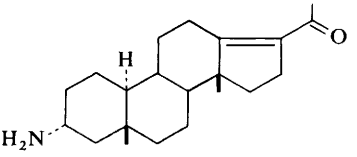


(102)

The presence of the dimethylamino-group appears to be responsible for the 10β configuration and the position of the C-8–C-9 double bond is due to the presence of the nitrogen heterocycle. It is very probable, from results obtained on other steroidal amines, that the configuration at C-14 has been inverted during the isomerisation and that it is, in fact, 14β.

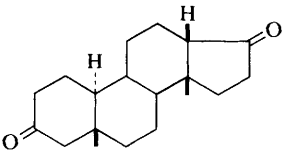


(103)



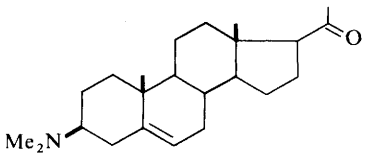
(104)

[88] S. Siddiqui, *Proc. Indian Acad. Sci.*, 1935, **2A**, 426.
[89] S. Siddiqui and S. K. Sharma, *J. Sci. Ind. Res., India*, 1945, **3**, 559.
[90] Ph. Devissaguet, M. Païs, F. X. Jarreau, Q. Khuong-Huu, and R. Goutarel, *Tetrahedron Letters*, 1966, 1073.
[91] M.-M. Janot, Ph. Devissaguet, M. Païs, Q. Khuong-Huu, F. X. Jarreau, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 4318.
[92] M.-M. Janot, Ph. Devissaguet, M. Païs, Q. Khuong-Huu, F. X. Jarreau, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 4323.

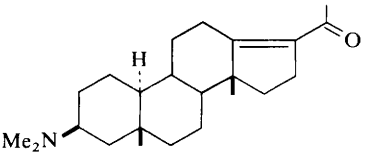


(105)

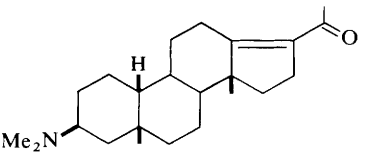
The rôle of the amino-group at C-3 is shown by the study of the rearrangement of the two alkaloids holamine (103) and methylholaphylline (106)[93,94] in sulphuric acid. On treatment with H_2SO_4, (103) gives the rearranged conjugated ketone (104), quantitatively. The structure of (104) is shown by its conversion into A-nor-D-homo-5β-androstane-3,16-dione (105), identical with the product prepared by Levisalles using another route.[95]



(106)



(107) (4%)

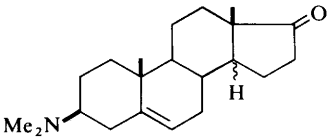


(108) (96%)

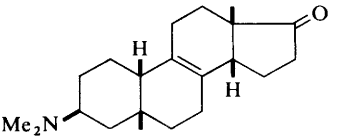
Methylholaphylline (106) gives the two rearranged ketones (107) and (108), with the latter predominating (96%). This shows that steric hindrance of the 3β-dimethylamino-group is responsible for the 10β configuration.

The two 3β-dimethylaminoandrost-5-en-17-ones, epimeric at C-14, namely (109), 14α, and (110), 14β, give the same 3β-dimethylamino-5β-methyl-14β-oestr-8-en-17-one (111) on treatment with H_2SO_4 at 0 °C. The 10β configuration of (111) is deduced from the negative circular dichroism curve of the ketol (112).

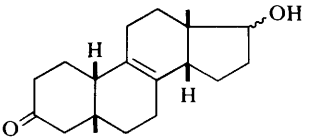
[93] F. Frappier, Q. Khuong-Huu, F. X. Jarreau, J. Hannart, and R. Goutarel, *Compt. rend.*, 1967, **264**, *C*, 1707.
[94] F. Frappier, Q. Khuong-Huu, and F. X. Jarreau, *Bull. Soc. chim. France*, 1969, 3265.
[95] J. Jacquesy, J. Levisalles, and J. Wagnon, *Chem. Comm.*, 1967, 25; *Bull. Soc. chim. France*, 1970, 670.



(109), 14α-H
(110), 14β-H



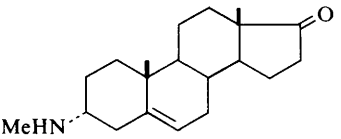
(111)



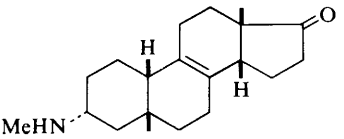
(112)

The rôle of the 17-keto-groups of (109) and (110) in stabilising the double bond at C-8–C-9 in the rearranged product (111) is comparable with that of the heterocycle in conessine. The formation of a 14β derivative from (109) indicates that C-14 is involved in the rearrangement in acid medium. The final product is considered thermodynamically more stable than the $\Delta^{8(14)}$ derivative.[96] Under the same conditions, the 3α-methylaminoandrost-5-en-17-one (113) gives an equilibrium mixture of the 10β and 10α derivatives, (114) and (115), in the ratio 55 : 45. Each of the compounds (114) and (115) gives the same equilibrium mixture when dissolved in H_2SO_4 at 0 °C.

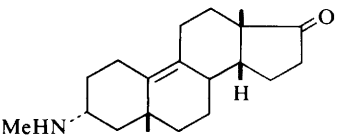
The isomerisation at C-10[96] can be explained by assuming the formation of a $\Delta^{9(10)}$ intermediate (116).



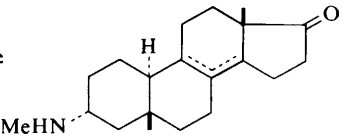
(113)



(114) (55%)



(116)

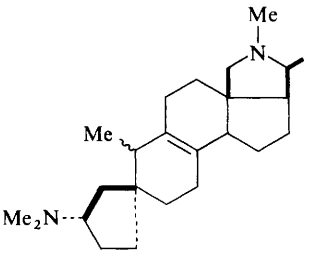


(115) (45%)

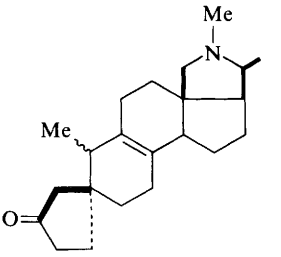
[96] F. Frappier, Thèse Dr. ès Sciences, Orsay, 19 Juin 1970.

It appears that these latter results constitute the first example of such an equilibrium during an acid-catalysed isomerisation reaction in the steroid series. Isomerisation of a double bond in a steroid system is equally possible from C-10 towards C-14, as well as from C-14 towards C-10. This confirms that it is impossible to predict the outcome of a 'backbone rearrangement' without taking into account the nature, the position, and the configuration of the groups present in the molecule.

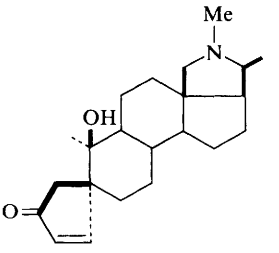
Treatment of conessine with a sulphuric acid–acetic acid mixture[89] gives neoconessine (117) as well as novoconessine (118).[97,98]



(117), 10β-H
(118), 10α-H



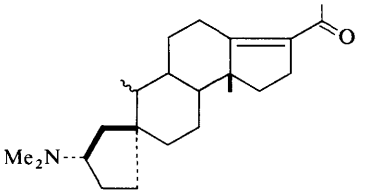
(119)
(120)



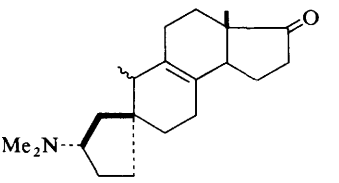
(121)

The n.m.r. spectra of (117) and (118) are characterised by the doublet arising from the methyl group at C-19. The position of the double bond is determined by the method of Castells and Meakins.[99] Replacement of the dimethylamino-group by a ketone function gives the cyclopentanones (119) and (120). These have also been prepared from the cyclopentenone (121), itself obtained by irradiation of holadienine (4) (cona-1,4-dien-3-one). On treatment with sulphuric acid–acetic acid at 0 °C, 3β-dimethylaminopregn-5-en-20-one (methylholaphylline, 106) and 3β-dimethylaminoandrost-5-en-17-one (109) give the analogues of neoconessine, (122) and (123), respectively.

[97] M.-M. Janot, Ph. Devissaguet, M. Païs, F. X. Jarreau, Q. Khuong-Huu, and R. Goutarel, *Tetrahedron Letters*, 1966, 4375.
[98] M.-M. Janot, Ph. Devissaguet, M. Païs, Q. Khuong-Huu, F. X. Jarreau, and R. Goutarel, *Bull. Soc. chim. France*, 1967, 4567.
[99] J. Castells and G. D. Meakins, *Chem. and Ind.*, 1956, 248.



(122)

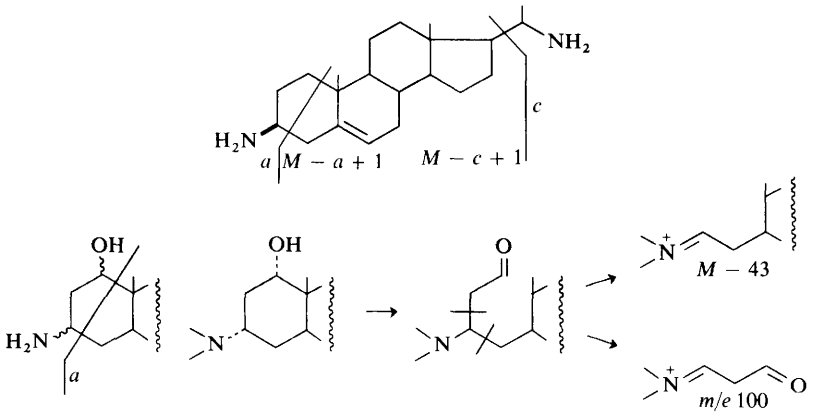


(123)

6 Mass Spectrometry of the Amino-steroids

Mass spectrometry has been widely used in the determination of the structures of the new steroidal alkaloids. The fragmentation pattern of 3-amino-steroids, 20-amino-steroids, and conanine derivatives has been described earlier.[1,2] Further interesting results have been published regarding 3,20-diaminopregn-5-enes[100,102] and 1-hydroxy-3-amino-steroids.[102,103]

A. 3,20-Diaminopregn-5-enes.—In addition to the classical ions *a* and *c*, the ions $(M - a + 1)$ and $(M - c + 1)$ are also observed. It is shown that this fragmentation implies the rearrangement of a hydrogen from one amino-group to another, one acting as donor, and the other as receiver (Scheme 5). The receiving group can be an amine, an amide, an imine, a nitrile, *etc.* The mobile hydrogen can come from an XH group (mobile hydrogen of an NH group, an OH group, and even a CH group). This phenomenon has not yet been fully explained, since the assumption of an interionic reaction could not be confirmed.[101]



Scheme 5

[100] P. Longevialle, *Chem. Comm.*, 1968, 545.
[101] P. Longevialle and L. Diatta, *Org. Mass. Spectrometry*, 1970, **3**, 803.
[102] P. Longevialle, *Compt. rend.*, 1967, **265**, *C*, 1337.
[103] P. Longevialle, *Tetrahedron*, 1969, **25**, 3075.

B. 1-Hydroxy-3-amino-steroids.—The presence of a hydroxy-group reinforces the importance of the ions *a* at the expense of the ions *b*. This effect is specially important in the case of the primary amines. Isomers with axial hydroxyl undergo a rearrangement before fragmentation, leading to the formation of characteristic ($M - 43$) ions. This stereoselectivity is also found in other epimeric steroidal alcohols.

Further information concerning the chemical shifts of 10- and 20-methyl groups (C-19 and C-21) can be found in an article[104] dealing with the n.m.r. spectra of many steroid derivatives, 18 → 20 lactones, 18 → 20 oxides, conanines, and heteroconanines.

PART II: Alkaloids of the Buxaceae

1 The *Buxus* Alkaloids

The elucidation of the structure of cyclobuxine-D[105] has marked the beginning of very active research on the alkaloids of several *Buxus* species. Many alkaloids have been described and most of them are included in 'The Alkaloids'.[2] This report deals only with the results obtained since 1966, arising out of the work of the research groups of Kupchan (*Buxus sempervirens*), Nakano (*Buxus microphylla* and *B. koreana*), Goutarel (*B. balearica*, *B. rolfei*, and *B. malayensis*) and, more recently, the German research group of Doepke.

Although some research chemists have not always followed the proposed system of nomenclature for these alkaloids, it may be worthwhile to recall it here. The system possesses the advantage of grouping bases of the same structural type. The *Buxus* alkaloids either contain one nitrogen atom or two nitrogen atoms. The nomenclature of alkaloids with two nitrogen atoms is given in Table 1, while that of alkaloids with one nitrogen atom is given in Table 2.[106]

Table 1 *Alkaloids with nitrogen at* C-3 *and at* C-20

	R^1	R^2	R^3	R^4
A	Me	Me	Me	Me
B	Me	Me	Me	H
C	H	Me	Me	Me
D	H	Me	Me	H
E	Me	Me	H	H
F	H	H	Me	Me
G	Me	H	H	H
H	H	H	H	Me
I	H	H	H	H

Table 2 *Alkaloids with nitrogen either at* C-3 *or at* C-20

	R^1	R^2	R^3	R^4
K	Me	Me	—	—
L	—	—	Me	Me
M	Me	H	—	—
N	—	—	Me	H
O	H	H	—	—
P	—	—	H	H

R^1, R^2: substituent at 3-N
R^3, R^4: substituent at 20-N

[104] J. C. Gramain, H.-P. Husson, and P. Potier, *Bull. Soc. chim. France*, 1969, 3585.
[105] K. S. Brown and S. M. Kupchan, *J. Amer. Chem. Soc.*, 1962, **84**, 4590, 4592.
[106] J. P. Calame, Thèse E.T.H. Zürich, 1965.

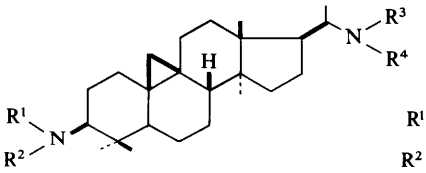
Buxus alkaloids belong to two structural types:

(I) Derivatives of 9β,19-cyclo-4,4,14α-trimethyl-5α-pregnane;
(II) Derivatives of *abeo*-9(10 → 19)-4,4,14α-trimethyl-5α-pregnane.

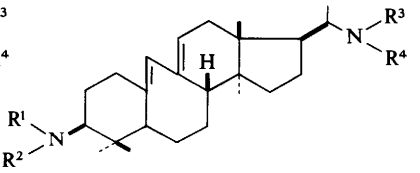
In each type, certain modifications are observed either due to the absence of one or both methyl groups, or due to the presence of a methylene group at C-4 and also the presence of different oxygen functions.

In general, alkaloids of type I include the prefix 'cyclo' in their names:

cycloprotobuxines: 4,4,14α-trimethyl, without any oxygen function.
cyclovirobuxines: 4,4,14α-trimethyl, 16α-hydroxy.
cyclovirobuxeines: 4,4,14α-trimethyl, 16α-hydroxy, Δ^6.
cyclomicrophyllines: 4α,14α-dimethyl, 4β-hydroxymethylene, 16α-hydroxy, Δ^6.
dihydrocyclomicrophyllines: 4α,14α-dimethyl, 4β-hydroxymethylene, 16α-hydroxy.
cyclobuxines: 4-methylene, 16α-hydroxy.
cyclobuxamines: 4α-methyl, 16α-hydroxy.



I



II

Since several newly-discovered alkaloids contain the 9β,19-cyclo-11-oxo conjugated system, it has been proposed to use the prefix 'cycloxo'[107,108] in naming them. Further, since many alkaloids contain the amide function, it has become customary to indicate this function in their names. Thus baleabuxine[2] and the baleabuxidines[109] are named as follows:

N-isobutyroylcycloxobuxine-F	4,4,14α-trimethyl, 11-oxo
N-benzoylcycloxobuxidine-F	4α,14α-dimethyl, 4β-hydroxymethylene, 11-oxo, 16α-hydroxy
N-isobutyroylcycloxobuxidine-F	

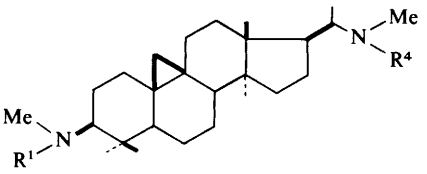
The alkaloids of type II are known as buxamines,[2] buxenines,[110] and buxidienines.[107]

[107] F. Khuong-Huu, D. Herlem-Gaulier, and R. Goutarel, *Bull. Soc. chim. France*, 1966, 3478.
[108] S. M. Kupchan, R. M. Kennedy, W. R. Schleigh, and G. Ohta, *Tetrahedron*, 1967, **23**, 4563.
[109] F. Khuong-Huu, D. Herlem-Gaulier, Q. Khuong-Huu, E. Stanislas, and R. Goutarel, *Tetrahedron*, 1966, **22**, 3321.
[110] R. T. Puckett, G. A. Sim, E. Abushanab, and S. M. Kupchan, *Tetrahedron Letters*, 1966, 3815.

Alkaloids containing one nitrogen atom are known by miscellaneous names for lack of a unified system of nomenclature.

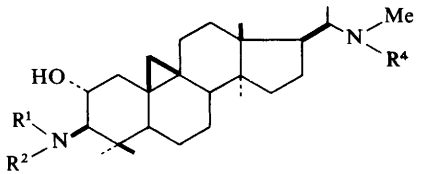
2 New Diamino-alkaloids

A. Alkaloids of Type I, not containing a Functional Group at C-11.—*N*-Acetylcycloprotobuxine-D (124), isolated from *B. sempervirens*,[108] gives on acetylation the already known *NN'*-diacetylcycloprotobuxine-D (125). Methylation (HCO_2H–HCHO) gives *N*-acetylcycloprotobuxine-B (126), which is different from the known *N*-acetylcycloprotobuxine-C (127). Deacetylation with lithium–ethylamine[111] has not been attempted.

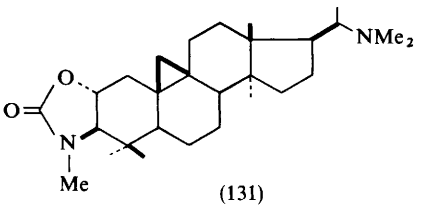


(124), R^1 = H, R^4 = Ac
(125), R^1 = R^4 = Ac
(126), R^1 = Me, R^4 = Ac
(127), R^1 = Ac, R^4 = Me

N-Benzoylcycloprotobuxolines-C (128) and -D (129), isolated from *B. sempervirens*,[108] are characterised by a 2α-hydroxy-group. The signal at 3.00 p.p.m. in their n.m.r. spectra gives evidence for restricted internal rotation.[112]



(128), R^1 = Me, R^2 = C_6H_5CO, R^4 = Me
(129), R^1 = Me, R^2 = C_6H_5CO, R^4 = H
(130), R^1 = Me, R^2 = H, R^4 = Me



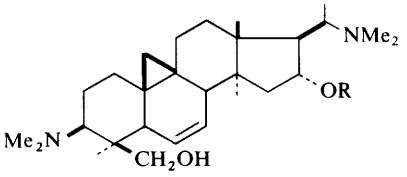
(131)

Alkaloid (129) could be a product of benzoylation of cyclovirobuxine-D, which carries a 16α-hydroxy-group, but the benzoylation of (129) gives an isomeric *NN'*-dibenzoyl derivative which is, however, not identical with *NN'*-dibenzoylcyclovirobuxine-D. Methylation of (129) gives (128). Alkaline hydrolysis of (128) and (129) gives cycloprotobuxoline-C (130) and cycloprotobuxoline-D,

[111] Q. Khuong-Huu, X. Monseur, M. Truong-Ho, R. Kocjan, and R. Goutarel, *Bull. Soc. chim. France*, 1965, 3035.
[112] J. M. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959, p. 336.

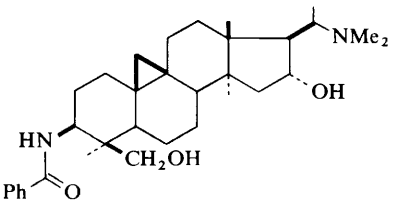
respectively. The ease of this hydrolysis is due to the proximity of the amide and alcohol functions ($N \rightarrow O$ acyl migration). In fact, treatment of (130) with phosgene in benzene gives the oxazolidone (131). Further, periodic acid oxidation of cycloprotobuxoline-D indicates the presence of the system —CHOH·CH(NHCH$_3$). Finally, chromic acid oxidation of (129) gives an amino-ketone (i.r. characteristic of a ketone in a six-membered ring). The n.m.r. spectrum of the *O*-acetyl derivative of (128) indicates a 2α-acetoxy-configuration.

Saponification of *O*-tigloylcyclovirobuxeine-D (132), isolated from *B. sempervirens*,[108] gives tiglic acid and cyclovirobuxeine-B (133). The n.m.r. spectrum shows features of *Buxus* alkaloids containing a Δ^6 double-bond[113,114] and indicates that the compound is a tiglic ester, and not an angelic ester which has isomerised in alkaline medium.

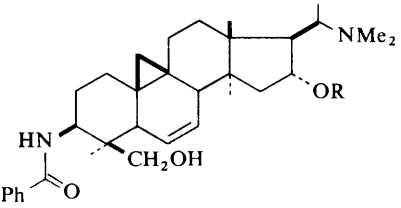


(132), R = —C(=O)—C(Me)=CH(Me)
(133), R = H

N-Benzoyldihydrocyclomicrophylline-F (134), isolated from *B. sempervirens*,[108] has been described under the name of buxepidine[115] and gives the already known dihydrocyclomicrophylline-F and benzoic acid on acid or alkaline hydrolysis. The ease of hydrolysis is again due to the proximity of the amide and alcohol functions.



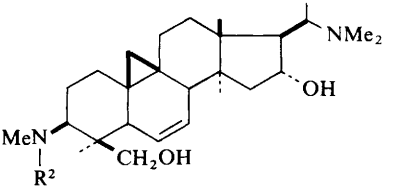
(134)



(135a), R = H
(135b), R = OAc

[113] T. Nakano and S. Terao, *J. Chem. Soc.*, 1965, 4512.
[114] D. Herlem-Gaulier, F. Khuong-Huu-Lainé, E. Stanislas, and R. Goutarel, *Bull. Soc. chim. France*, 1965, 657.
[115] W. Döpke and B. Müller, *Pharmazie*, 1967, **21**, 666.

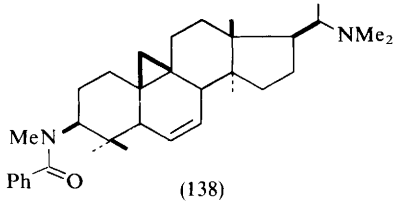
Cyclomicrosine-C (136), isolated from *B. microphylla* Sieb. et Zucc. var. *suffruticosa* Makino,[116] is prepared by benzoylation of cyclomicrophylline-C, and is therefore *N*-benzoylcyclomicrophylline-C.



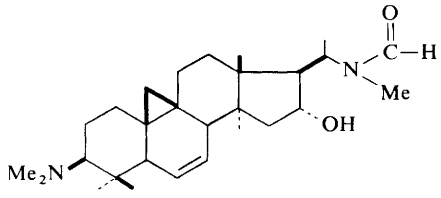
(136), $R^2 = C_6H_5CO$·
(137), $R^2 = H$

N-Benzoylcyclomicrophylline-F and *O*-acetyl-*N*-benzoylcyclomicrophylline-F, isolated from *B. sempervirens*,[117—119] have been described under the names of buxidine (135a) and buxandrine (135b). Methylation of (135a) (HCO_2H–HCHO) gives cyclomicrosine-C (136),[116] while hydrolysis (dilute HCl) gives cyclomicrophylline-C (137).[120] Catalytic hydrogenation of (135a) gives buxepidine (134).

N-Benzoylcycloprotobuxeine-C (138), from *B. sempervirens*, has been described under the name of buxeridine.[121] Its structure was established from i.r. and mass-spectral data.

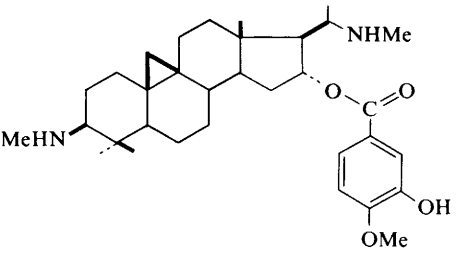


(138)



(139)

[116] T. Nakano, S. Terao, and Y. Saeki, *J. Chem. Soc. (C)*, 1966, 1412.
[117] W. Döpke and B. Müller, *Naturwiss.*, 1965, **52**, 61.
[118] W. Döpke and B. Müller, *Pharmazie*, 1966, **21**, 769.
[119] W. Döpke, B. Müller, G. Spiteller, and M. Spiteller-Friedmann, *Tetrahedron Letters*, 1967, 4247.
[120] S. Terao and T. Nakano, *Tetrahedron Letters*, 1964, 1045.
[121] W. Döpke, B. Müller, G. Spiteller, and M. Spiteller-Friedmann, *Naturwiss.*, 1967, **54**, 200.

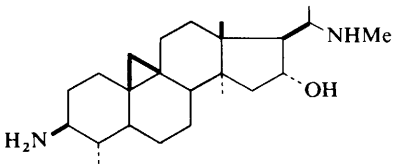


(140)

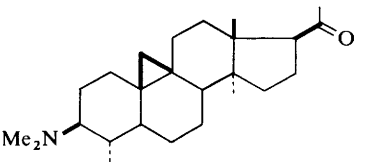
N-Formylcyclovirobuxeine-B (139), isolated from *B. malayana* Ridl,[122] shows a signal at −0.23 p.p.m. in its n.m.r. spectrum, corresponding to a cyclopropanic methylene group in alkaloids with a Δ^6 double-bond.[113,114] The n.m.r. spectrum also shows two singlets of the two rotamers of an *N*-methylformamido-group at 8.05 and 8.11 p.p.m. Saponification (KOH–EtOH) gives cyclovirobuxeine-B, which can be formylated to (139).

O-Vanilloylcyclovirobuxine-D (140), isolated from *B. malayana*,[122] gives cyclovirobuxine-D and vanillic acid on saponification.

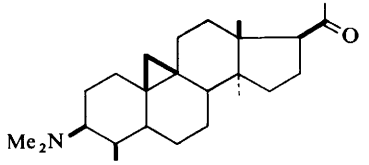
Cyclobuxamine-H (141), isolated from *B. sempervirens*, has been described as 4β-methyl,[123,124] but its structure was revised by Nakano,[116] who suggested a 4α-methyl configuration which is more usual for natural products. In fact, in the n.m.r. spectrum of (141) and in that of other alkaloids having a single methyl group at C-4, the cyclopropane methylene group gives an AB quartet with chemical shifts of 0.09—0.18 p.p.m. and 0.33—0.50 p.p.m. In synthetic derivatives with



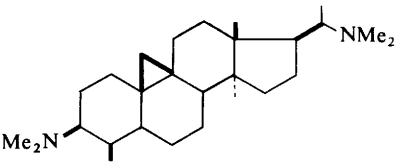
(141)



(142)



(143)



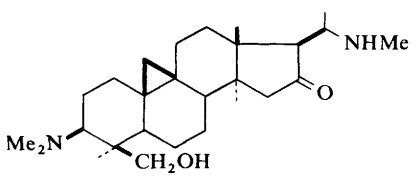
(144)

[122] F. Khuong-Huu and M. J. Magdeleine, *Ann. pharm. franç.*, 1970, **23**, 211.
[123] K. S. Brown and S. M. Kupchan, *Tetrahedron Letters*, 1964, 2895.
[124] K. S. Brown and S. M. Kupchan, *J. Amer. Chem. Soc.*, 1964, **86**, 4414.

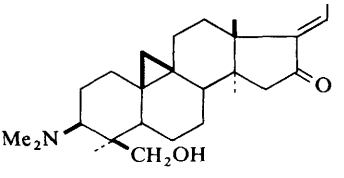
a 4β-configuration, the shifts are observed at 0.28—0.38 p.p.m. and 0.59—0.63 p.p.m. (0.20 and 0.29 p.p.m. downfield shift). On the other hand, the cyclopropane methylene group in the 4,4-dimethyl derivatives gives the same signals (0.63 and 0.28 p.p.m.) as those of the synthetic 4β-methyl derivatives. The 4α-methyl configuration of cycloeucalenol being known, its 3α- and 3β-amino-derivatives have been prepared. The configuration of the amino-group at C-3 has only a small influence on the chemical shift of the cyclopropane methylene group. The effect of the orientation of the methyl group at C-4 on this shift is shown by examination of the n.m.r. spectra of 3β-dimethylamino-9β,19-cyclo-4α,14α-dimethyl-5α-pregnan-20-one (142) and 3β-dimethylamino-9β,19-cyclo-4β,14α-dimethyl-5α-pregnan-20-one (143). The signals of the methyl group at C-4 in the different 4α- and 4β-methyl-steroids are respectively at 0.95 and 0.90 p.p.m. and at 0.78 and 0.88 p.p.m. (*d*, $J = 6.5$ Hz).

The structure of buxocyclamine-A (144), from *B. sempervirens*,[125] was assigned on the basis of i.r. and mass spectra. No arguments have been given in support of the 4β-methyl configuration suggested.

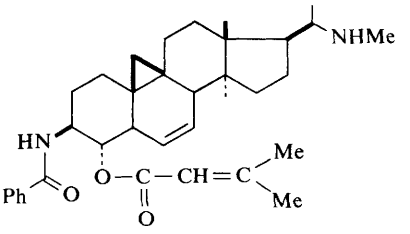
Buxazidine-B (145), also isolated from *B. sempervirens*,[121] possesses a primary alcohol group and a keto-group. It has been assigned structure (145) on the basis of i.r. and mass spectra, as well as certain chemical reactions which are not described. This structure, if it is correct, would be particularly interesting as it corresponds to a 16-oxo-dihydrocyclomicrophylline which, in alkaline medium, easily gives (146), containing one nitrogen atom and the 17-en-16-one system.



(145)



(146)

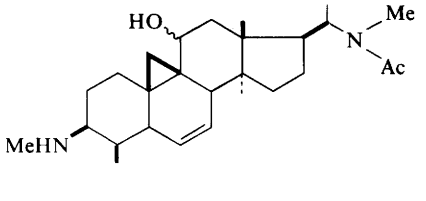


(147)

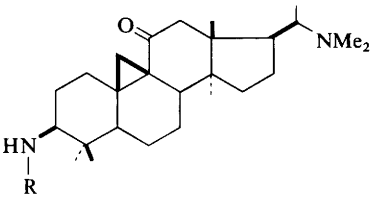
[125] W. Döpke, B. Müller, and P. W. Jeffs, *Pharmazie*, 1968, **23**, 37.

The i.r. spectrum of buxaltine (147), isolated from *B. sempervirens*,[126] indicates ester, cyclopropane, and benzamide groups, while the mass spectrum indicates an NHMe group at C-20 and a benzamido-group. The presence of a Δ^6 double-bond is shown by the difference in molecular rotation between (147) and its dihydrogenated derivative.

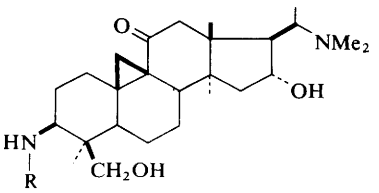
The structure of buxiramine (148), isolated from *B. sempervirens*,[126] is established from its mass, i.r., and n.m.r. spectra. No proof has been given either for the 4β-methyl group or for the position of the hydroxy-group. Analogy with 11-keto-alkaloids is the only point in favour of this structure



(148)



(149)



(150)

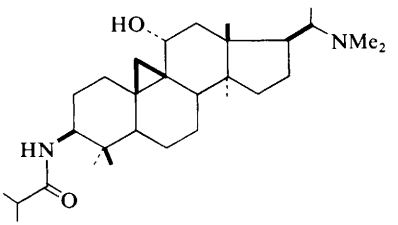
B. Alkaloids of Type I, containing a Functional Group at C-11.—The first alkaloid of this type, isolated from *B. balearica*, was named baleabuxine.[127,128] It was later known as *N*-isobutyroylbaleabuxine-F.[109] Since the keto-group was shown to be at C-11.[107,127] baleabuxine is named as *N*-isobutyroylcyclobuxine-F (149, R = $Me_2CH{\cdot}CO{\cdot}$). In the same way, baleabuxidine[127] (*N*-isobutyroyl-baleabuxidine-F[109]) should be named as *N*-isobutyroylcycloxobuxidine-F (150, R = $Me_2CH{\cdot}CO{\cdot}$). The ketone function in alkaloids containing the conjugated 9β,19-cyclo-11-keto-system is characterised by (i) i.r. spectra (C=O at 1670 cm^{-1} in $CHCl_3$ and at 1685 cm^{-1} in Nujol mull or KBr), (ii) u.v. spectra (λ_{max} 217—219 nm; ε 6000—8000), (iii) circular dichroism (λ_{max} 293, 301, 311, 322 nm, $\Delta\varepsilon$ + 0.82, +0.94, +0.82, +0.41). The signals of the cyclopropane methylene groups are

[126] W. Döpke and B. Müller, *Pharmazie*, 1969, **24**, 649.
[127] D. Herlem-Gaulier, F. Khuong-Huu-Lainé, E. Stanislas, and R. Goutarel, *Bull. Soc. chim. France*, 1965, 657.
[128] F. Khuong-Huu-Lainé, D. Herlem-Gaulier, and R. Goutarel, *Compt. rend.*, 1965, **261**, 4139.

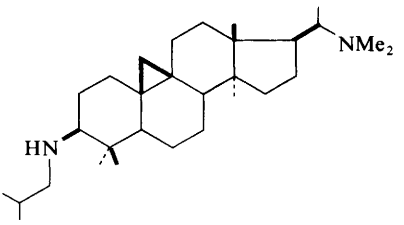
not visible, and are only observed on reduction ($LiAlH_4$) of the keto-group; the methylene group at C-12 appears as a broad singlet at 2.43 p.p.m. The cyclopropane ring is shown by a band at 3.30 μm in its i.r. spectrum and also by a band at 12 μm, the latter always being present in alkaloids containing the conjugated cyclopropane-ketone system.[108]

Reactivity of the 9β,19-Cyclo-11-keto Conjugated System.[107,129] The reactivity of this system has been studied in the case of the cycloxobuxines (149) and the cycloxobuxidines (150):

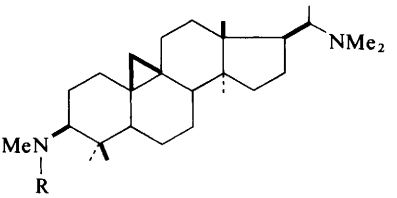
(i) *Reduction by* $LiAlH_4$. Reduction of (149, R = Me_2CHCO·) in ether at laboratory temperature gives the alcohol (151). Reduction in dioxan at 100 °C gives two compounds, one an alcohol and the other the product of hydrogenolysis in which the amide group is reduced to (152); this reaction has enabled correlation with cycloprotobuxine-C (153, R = H).



(151)



(152)



(153)

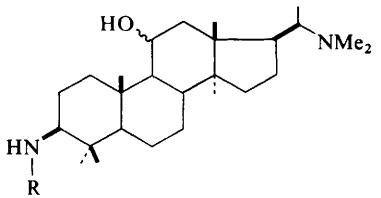
Cycloprotobuxine-C (153, R = H) was converted into the amide (153, R = Me_2CHCO), and this was reduced to give (153, R = Me_2CHCH_2·), identical with the methylation product (HCO_2H–HCHO) of (152). The cyclopropane methylene signals (AB; J = 5 Hz; 0.28 and 0.54 p.p.m.) become clearer in the n.m.r. spectrum of (152).

The proportion of (152) increases with the period of heating in dioxan, becoming almost total after 96 h. However, it does not appear that (152) is produced from the hydrogenolysis of an alcohol formed earlier, as (151) does not give (152) under the same conditions.[108]

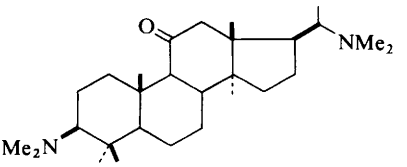
[129] D. Herlem-Gaulier, F. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1968, 763.

Reduction of *N*-isobutyroylcycloxobuxidine-F (150, R = Me_2CHCO·) in $LiAlH_4$–dioxan at 100 °C also causes elimination of the keto-group. Since cycloxobuxidine-F (150, R = H) is easily obtained by acid or alkaline hydrolysis of the amide function, reduction by $LiAlH_4$ gives dihydrocyclomicrophylline-F directly.

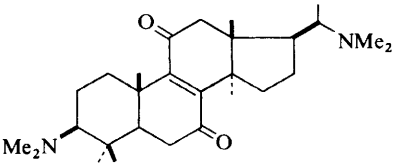
(ii) *Reduction by sodium–propanol.* On treatment with sodium in boiling propanol, *N*-isobutyroylcycloxobuxine-F (149, R = Me_2CHCO) gives two compounds resulting from the opening of the cyclopropane ring by rupture of either the 9,19 bond or the 9,10 bond. The product of rupture of the 9,19 bond, (154), contains an alcohol function at C-11 and a methyl group at C-10. Compound (154) has been used to correlate the cycloxobuxines with cycloprotobuxine A, thereby definitely fixing the earlier described[2] position of the keto-group in (149).[128] Treatment of (154) with lithium–ethylamine[111] gives the primary amine (155), which is methylated and then oxidised to (156). Cycloprotobuxine-A has been isomerised ($CHCl_3$–HCl) with opening of the cyclopropane ring at 9,19 to give a mixture of compounds with a methyl group at C-10 and a double bond at C-7, -8, or -9. Oxidation of this mixture gives the enedione (157), which gives (156) after Wolff–Kishner elimination of the keto-group at C-8, lithium–liquid ammonia reduction of the double bond, and oxidation.



(154), R = Me_2CHCO·
(155), R = H



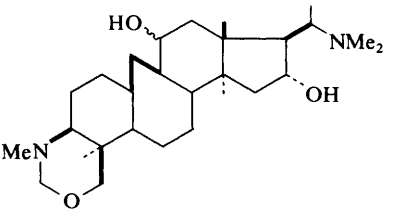
(156)



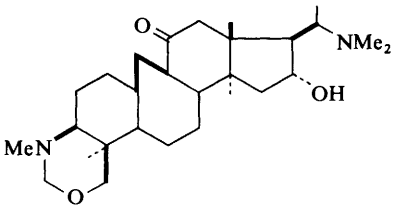
(157)

N-Isobutyroylcycloxobuxidine-F (150, R = Me_2CHCO·), when treated with sodium in boiling propanol, gives mainly the compound resulting from opening of the 9,10-bond of the cyclopropane. Under these conditions, the amide function is hydrolysed (*N* → *O* acyl migration). Since the primary amine product of reaction cannot be easily isolated, it has been treated with the HCO_2H–HCHO mixture to give a product (158) of the *abeo*-9(10 → 19)-pregnane type. Oxidation

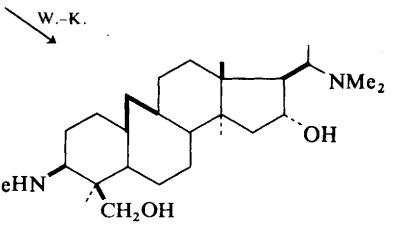
of the 11-hydroxy-group gives the ketone (159), which is reduced by the Wolff–Kishner method to (160).



(158)



(159)

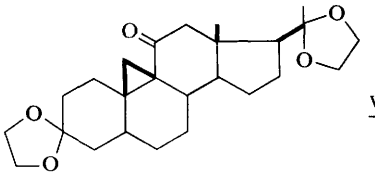


(160)

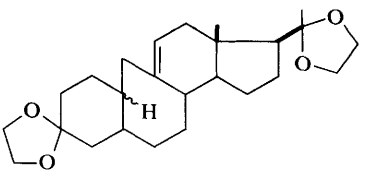
(iii) *Wolff–Kishner reduction of the 9β,19-cyclo-11-keto system.* Kupchan[130] suggested the formation of a carbanion intermediate at C-10 for the mechanism of the Wolff–Kishner reduction of the ketone (161). Opening of the cyclopropane ring gives two compounds (162), epimeric at C-10 and containing a 9,11 double-bond. It has been shown[131] that, since the 11-keto-group is too sterically hindered, the hydrazone intermediate in the Wolff–Kishner reaction of the cycloxobuxines and cycloxobuxidines can only be formed after opening of the cyclopropane ring. The opening of the cyclopropane ring is thermal.[132] Compound (165), with the double bond at C-1, is obtained from (149, R = Me_2CHCO·) through (163) and (164).

Reduction of (150, R = Me_2CHCO·), under the alkaline conditions of the Wolff–Kishner reaction, is accompanied by hydrolysis of the amido-group. The amine (166) is obtained along with (167), a product of cyclisation of the

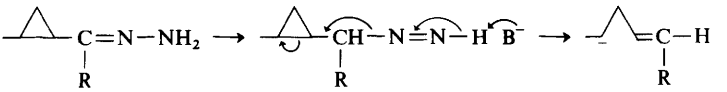
[130] S. M. Kupchan, E. Abushanab, K. T. Shanasundar, and A. W. By, *J. Amer. Chem. Soc.*, 1967, **89**, 6327.
[131] F. Khuong-Huu, D. Herlem, and J. J. H. Simes, *Bull. Soc. chim. France*, 1969, 258.
[132] G. Ohloff, *Tetrahedron Letters*, 1965, 3795.

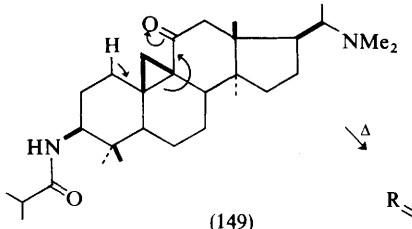


W.-K.?



(161) (162)





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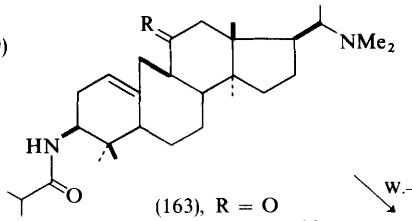
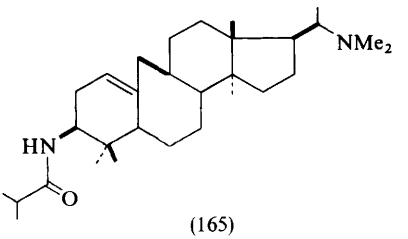
(149)



W.-K.

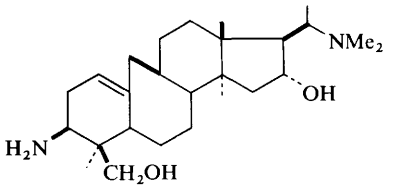
(163), R = O
(164), R = N—NH2



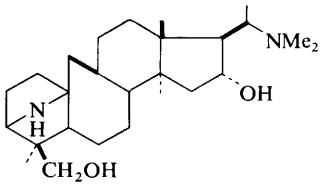
(165)

3-amino-group onto C-10. Reduction of (166) gives (160), also obtained by opening of the cyclopropane ring with sodium and boiling propanol.

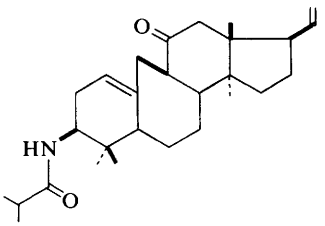
(iv) *Pyrolysis of derivatives of* N-*isobutyroylcycloxobuxine-F and* N-*isobutyroylcycloxobuxidine-F*. Since the cyclopropane ring of *N*-isobutyroylcycloxobuxine-F opens on heating in alkaline medium, the neutral compound 'baleabuximethine'[127] has the structure (168). A basic compound (169) is also formed at



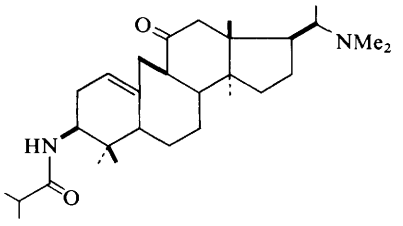
(166)



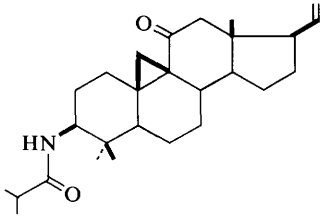
(167)



(168)



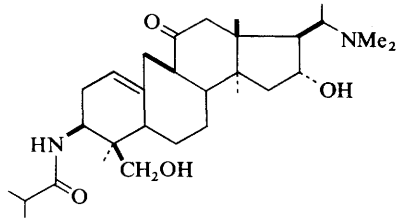
(169)



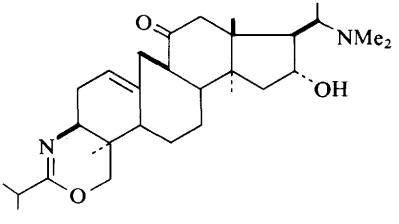
(170)

the same time. *N*-Isobutyroylcycloxobuxine-F can be sublimed under vacuum (200 °C; 0.01 mm Hg) without opening the cyclopropane ring. Compound (170) was obtained by pyrolysis of the *N*-oxide of *N*-isobutyroylcycloxobuxine-F.

On the other hand, sublimation of *N*-isobutyroylcycloxobuxidine-F, under high vacuum, leads to the ring-opened product (171). A dihydro-oxazine (172) is obtained when sublimation is carried out in the presence of a base (tetramethylammonium hydroxide).

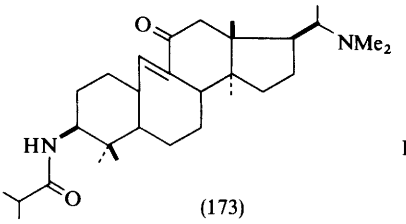


(171)

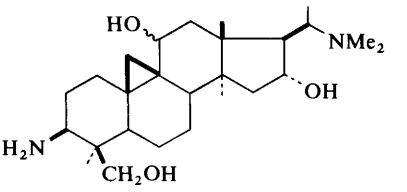


(172)

(v) *Isomerisation in acid medium.* A mixture of unidentifiable products is all that is obtained when the cyclopropane ring of the 9β,19-cyclo-11-keto-derivatives is opened by the classical method using HCl–$CHCl_3$. Reaction with boron trifluoride–C_6H_6 gives the compound (173), formed by cleavage of the 9,10 bond. Compound (173) is characterised by a signal at 6.56 p.p.m. in its n.m.r. spectrum, due to an olefinic proton β to a ketone.



(173)



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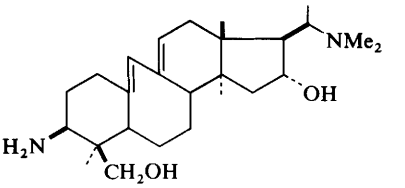


(175)

An interesting correlation between the cycloxobuxidines and the buxidienines has been established.[129,133] The alcohol (174), obtained by controlled reduction ($LiAlH_4$) of cycloxobuxidine-F, gives the buxidienine-F (175) when treated with sulphuric acid–dioxan–water.

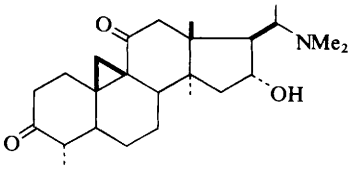
Cycloxobuxines (149). *N*-Isobutyroylcycloxobuxine-F (R = Me_2CHCO·), isolated from *Buxus balearica*, has been described as baleabuxine.[2] Recently, it has been isolated by Russian workers[134] from the same *Buxus* species.

N-Benzoylcycloxobuxine-F (R = C_6H_5CO·), isolated from *B. sempervirens*,[108] has also been described as buxatine.[135]

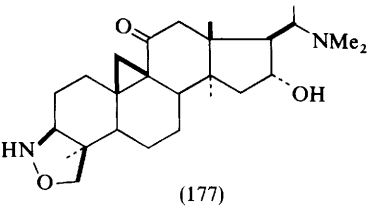
Cycloxobuxidines (150). The presence of a 4β-hydroxymethylene group and a 16α secondary alcohol group imparts to cycloxobuxidines the special characteristics of alkaloids containing these functional groups, such as the cyclomicrophyllines.[2] $N \rightarrow O$ Acyl migration accounts for the easy hydrolysis of the amide alkaloids to the corresponding amines. The proximity of the amine and primary alcohol groups brings about ready cyclisation.

[133] D. Herlem, F. Khuong-Huu, and R. Goutarel, *Compt. rend.*, 1967, **264**, *C*, 798.
[134] I. O. Kurakina, N. F. Proskurnina, and A. V. Stepanyants, *Khim. prirod. Soedinenii*, 1969, 406.
[135] W. Döpke and B. Müller, *Naturwiss.*, 1967, **54**, 249.

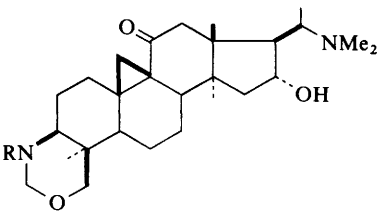
Ruschig deamination[48] of cycloxobuxidine-F gives two compounds. One of these, (176), is the ketonic product of retroaldolisation, while the other, (177), is an isoxazolidine formed from the chloramine intermediate.[129,136]



(176)

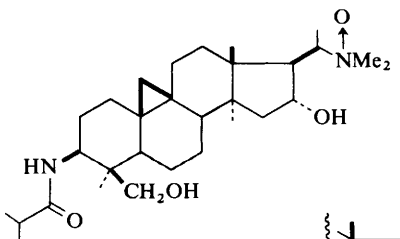


(177)

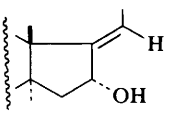


(178)

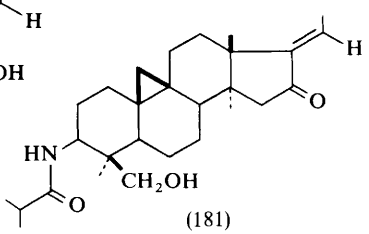
The cycloxobuxoxazines (178) are easily obtained by heating cycloxobuxidine-F with formaldehyde in dioxan, or by treatment with HCO_2H–HCHO. The tertiary amino-group of *N*-isobutyroylcycloxobuxidine-F cannot be eliminated by the Hofmann method.[136] The 16α-OH hinders the formation of an iodomethylate. The *N*-oxide (179) has been obtained by the action of *p*-nitroperbenzoic acid in methylene dichloride. It has been shown earlier that the



(179)



(180)

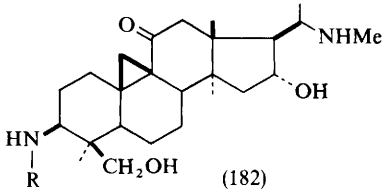


(181)

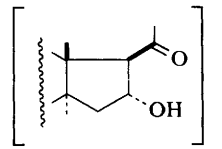
[136] F. Khuong-Huu, D. Herlem, and A. Milliet, *Bull. Soc. chim. France*, 1969, 256.

pyrolysis of cycloxobuxidines leads to opening of the cyclopropane ring by cleavage of the 9,10 bond. However, when the aminoxide (179) is heated at 90 °C–0.01 mmHg, the allylic alcohol (180) is obtained. It can be oxidised to (181). Since elimination in the Cope reaction[137] involves a cyclic mechanism, (181) is the *cis*-17-en-16-one. This configuration is observed in many *Buxus* alkaloids containing one nitrogen atom.

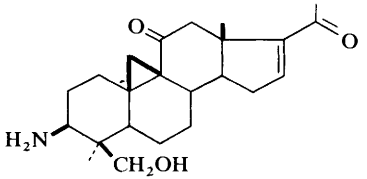
Deamination of 20α-dimethylamino-16-keto-derivatives in alkaline medium gives a mixture of the 17-*cis*- and 17-*trans*-enones.[124] Under Ruschig reaction conditions, *N*-isobutyroylcycloxobuxidine-H (182, R = Me_2CHCO·) gives the ketol (183), which readily dehydrates to the Δ^{16}-20-keto-derivative (184).[129]



(182)



(183)



(184)

N-Isobutyroylcycloxobuxidine-F (150, R = Me_2CHCO·), isolated from *Buxus balearica*, has been described as baleabuxidine and later as *N*-isobutyroylbaleabuxidine-F.[109]

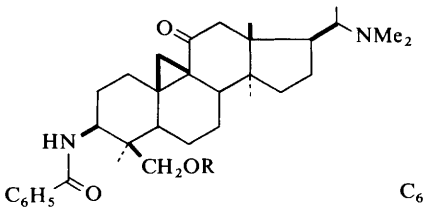
N-Benzoylcycloxobuxidine-F (150, R = C_6H_5CO·), has been isolated from *B. balearica*[109,129] and *B. sempervirens*,[108] and *N*-isobutyroylcycloxobuxidine-H (182, R = Me_2CHCO·), has been isolated from *B. balearica*.[129]

N-Benzoylcycloxobuxoline-F (185) and *O*-acetyl-*N*-benzoylcycloxobuxoline-F (186)[129] have been isolated from *B. sempervirens* and are characterised by the presence of a 4β-hydroxymethylene group.[108]

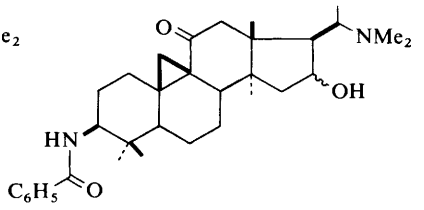
Buxarine (187), isolated from *B. sempervirens*,[138] is characterised by a secondary alcohol group which, from the chemical shift of the 16β proton, should be 16α. It should be named as *N*-benzoylcycloxovirobuxine-F.

Cycloxobuxoxazine-C (178, R = H), isolated from *B. balearica*,[129] has been described as baleabuxoxazine.[109] It can be obtained on treatment of cycloxo-

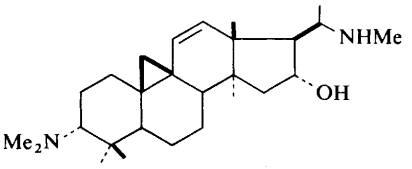
[137] A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, 1953, **75**, 3212.
[138] W. Döpke, B. Müller, and P. W. Jeffs, *Pharmazie*, 1966, **21**, 643.



(185), R = H
(186), R = Ac



(187)

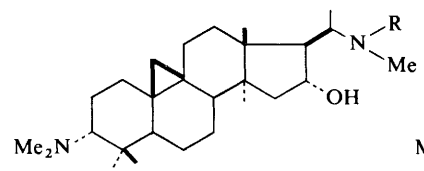


(188)

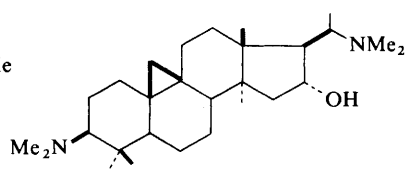
buxidine-F with formaldehyde in dioxan. Methylation of cycloxobuxidine-H with HCO_2H–HCHO gives cycloxobuxoxazine-A (178, R = Me).

Cyclokoreanine-B (188), from *B. koreana*,[139] is characterised by the presence of a Δ^{11} double-bond conjugated to the cyclopropane ring. The mass spectrum indicates a 20-NHMe group as well as a 3-NMe_2 group. The n.m.r. signal of one of the protons of the cyclopropane ring is seen at 0.45 p.p.m. (J = 4 Hz). The AB quartet of two olefinic protons, the signals of four tertiary methyl groups, one secondary methyl group, one NMe_2 group, and one NMe group can also be seen. The 16β-H linked to the 16α-OH appears as a sextet at 4.20 p.p.m. (J = 2.7, 6.7, and 9.0 Hz). Attempted methylation with HCO_2H–HCHO opens the cyclopropane ring and gives an amorphous mixture. Methylation with CH_3I–acetone, followed by addition of ethylamine, gives cyclokoreanine-A. Oxidation (CrO_3–AcOH) of (188) gives a 20α-methylamino-16-ketone, which is deaminated by activated neutral alumina to give the unsaturated $\alpha\beta$-*cis*-cisoid cyclopentenone as sole product.

Catalytic hydrogenation of cyclokoreanine-B gives dihydrocyclokoreanine-B (189, R = H), which can be methylated with HCO_2H–HCHO to dihydrocyclokoreanine-A (189, R = Me). The difference in molecular rotation between the



(189)



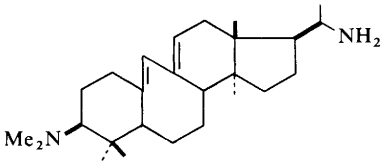
(190)

[139] T. Nakano, S. Terao, Y. Saeki, and K. D. Jin, *J. Chem. Soc. (C)*, 1966, 1805.

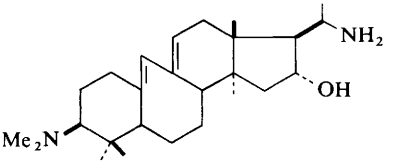
cyclokoreanines and dihydrokoreanines ($\Delta[M]_D = +168°$) fits in with a Δ^{11}-steroid. Dihydrocyclokoreanine-A is different from cyclovirobuxine-A (190), and the 3α-dimethylamino-configuration is suggested for cyclokoreanine-B.

C. Alkaloids of Type II.—Two alkaloids of this type, buxamine-E (buxenine-E, 191)[2] and buxaminol-E (192),[2] were isolated from the leaves of *B. balearica*.[109] Two other alkaloids have also been described.

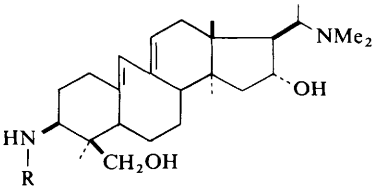
N-Isobutyroylbuxidienine-F (193, R = Me_2CHCO·), isolated from *B. balearica*,[107] is also known as *N*-isobutyroylbaleabuxidienine-F,[109] and is characterised by a conjugated heteroannular diene system of the same type as that of buxamine-E and buxaminol-E. Both this alkaloid and *N*-benzoylbuxidienine-F



(191)

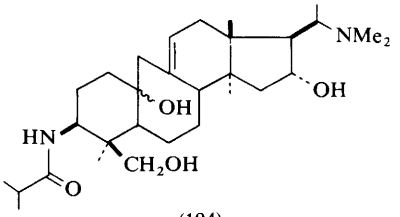


(192)



(193)

(193, R = C_6H_5CO·), isolated from *B. balearica*[107,109] and *B. sempervirens*,[108] give buxidienine-F (175) on hydrolysis. The presence of a secondary alcohol group is shown by oxidation to a cyclopentenone, which gives the *cis*- and/or *trans*-cisoid-cyclopentenone on deamination in alkaline medium. A correlation between cycloxobuxidine-F and buxidienine-F (175) has been established.[129,133]



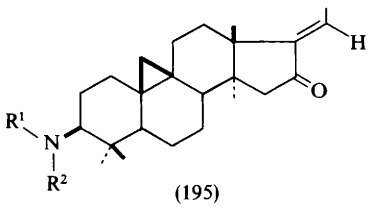
(194)

N-Isobutyroylbuxaline-F (194)[107] (*N*-isobutyroylbaleabuxaline-F[109]), isolated from *B. balearica*, is related to the buxidienines. It is transparent in the u.v. above 220 nm, and n.m.r. indicates the presence of a single ethylenic proton. The fourth oxygen atom is part of a tertiary alcohol function and gives a diene of the buxidienine type on dehydration. This structure requires confirmation.

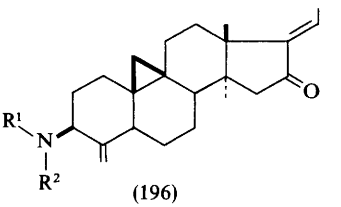
3 New Monoamino-alkaloids

Monoamino-alkaloids have been isolated, in general, from the feebly basic fractions. It was in this way that Voticky and Tomko[144] isolated an amino-pregnane, irehine, from the leaves of *B. sempervirens*. Irehine was earlier extracted from the leaves of an Apocynacea, *Funtumia elastica*.[140] Other alkaloids isolated from different *Buxus* species are derivatives of methyl-pregnanes, and a few amongst them have been already described.[2]

A. Derivatives Aminated at C-3.—The spectral data of cyclobuxophylline (195, $R^1 = R^2 = Me$), isolated from *B. microphylla* Sieb. et Zucc. var *suffruticosa* Makino *forma major* Makino,[116] indicate the presence of a *cis*-$\alpha\beta$-unsaturated cyclopentenone. Cyclobuxophylline has been prepared from cyclovirobuxine-A, itself obtained by elimination of the primary alcohol function of dihydrocyclo-microphylline-A. Oxidation of cyclovirobuxine gives a 16-keto-derivative, while passage over activated neutral alumina gives cyclobuxophylline by deamination at C-20.



(195)



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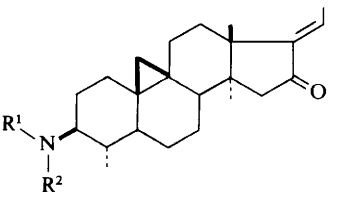


(197)

[140] M. Truong-Ho, X. Monseur, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1963, 2332.
[141] W. Döpke, R. Haertel, and H. W. Fehlhaber, *Tetrahedron Letters*, 1969, 4423.
[142] T. Nakano and Z. Voticky, *J. Chem. Soc. (C)*, 1970, 590.
[143] C. Djerassi, 'Optical Rotatory Dispersion,' McGraw-Hill, New York, 1960, p. 90.
[144] Z. Voticky and J. Tomko, International Symposium, Halle (Saale) 1965, June 24—27; *Abh. Deutsch. Akad. Wissensch. Berlin*, 1966, **3**, 93.

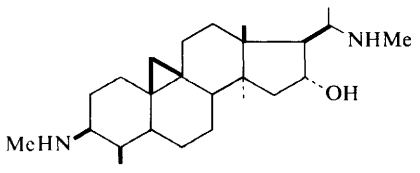
Cyclobuxophylline (195, R^1 = Me, R^2 = H), isolated from *B. microphylla*,[116] has also been isolated from *B. sempervirens* and known as buxenone.[138] It is methylated by CH_3I to cyclobuxophylline, while benzoylation affords[118] the non-basic buxanine (195, R^1 = Me, R^2 = C_6H_5CO·).

Buxene (195, R^1 = H, R^2 = C_2H_5OCO·) and methylbuxene (195, R^1 = Me, R^2 = C_2H_5OCO·), two feebly basic alkaloids, have been extracted from *B. sempervirens*[141] and possess an interesting urethane function at C-3β. Methylbuxene has been obtained on treatment of the buxenone (195, R^1 = Me, R^2 = H) with ethyl chloroformate.

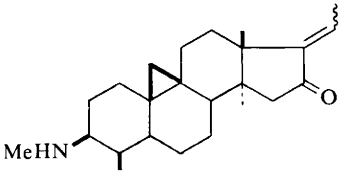
Cyclosuffrobuxinine (196, R^1 = Me, R^2 = H) and cyclosuffrobuxine (196, R^1 = R^2 = Me) have been isolated from *B. microphylla*.[116] Cyclosuffrobuxinine can be obtained by oxidation (CrO_3–CH_3CO_2H) of cyclobuxine-D to a cyclopentenone, which is deaminated at C-20 by treatment with neutral alumina giving only the *cis*-$\alpha\beta$-unsaturated cyclopentenone. Methylation of cyclosuffrobuxinine with CH_3I gives cyclosuffrobuxine.

Cyclobuxosuffrine (197, R^1 = Me, R^2 = H), isolated from *B. microphylla*,[116] has been correlated with cyclobuxine-D.[142] Oxidation (CrO_3–CH_3CO_2H) of dihydrocyclobuxine-D (198, 4β-methyl) gives a cyclopentenone which on treatment with alkali eliminates a 20-amino-group, giving a mixture (199) of $\alpha\beta$-unsaturated cyclopentenones. The double bond is hydrogenated and the keto-group reduced to alcohol by $LiAlH_4$. Ruschig deamination[48] at C-3 gives the ketol (200), the treatment with alkali epimerising the methyl group at C-4 from axial to equatorial. The 3β-dimethylamino-group is introduced by reduction of the oxime of (200) and methylation. Finally, the 16-hydroxy-group is oxidised. The product obtained is identical with dihydromethylcyclobuxosuffrine, which possesses the 4α-methyl configuration of natural products monomethylated at C-4.

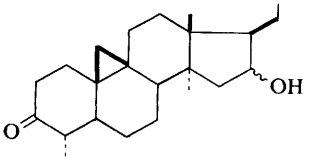
The spectral data of cyclomicrobuxeine (202), isolated from *B. microphylla*,[116] indicate that the compound is a cisoid-$\alpha\beta$-unsaturated ketone. It has been obtained by dehydration of the 16α-OH group of cyclomicrobuxine (201).[2]



(198)



(199)



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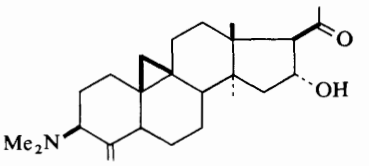
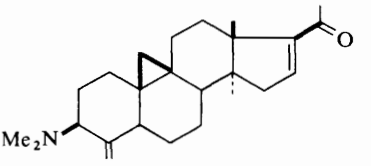


(201)



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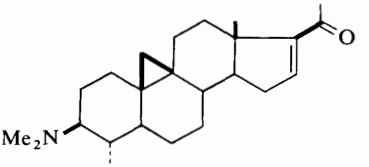
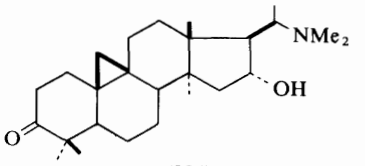
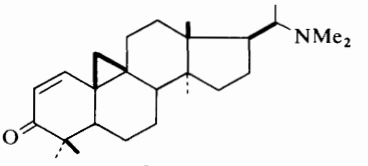


(203)

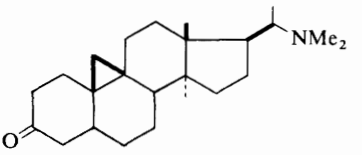
Cyclobuxomicreine (203), isolated from *B. microphylla*,[116] exhibits an n.m.r. spectrum which suggests that this alkaloid is a dihydrocyclomicrobuxeine, and the 4α-methyl configuration is shown, as in cyclobuxamine-H. Catalytic reduction of (203) gives the derivative (142, 4α-methyl). The derivative (149, 4β-methyl) was obtained from cyclomicrobuxine (201) by dehydration of the 16α-OH group and catalytic reduction.



(204)



(205)



(206)

B. Alkaloids Aminated at C-20.—The i.r. spectrum of cyclomikuranine (204), isolated from *B. microphylla*,[116] shows a six-membered-ring ketone, and the mass spectrum shows a 20-dimethylamino-group. The negative Cotton curve is typical of a 4,4-dimethyl-3-oxo-5α-steroid.[143] N.m.r. indicates an NMe_2 group as well as a 16α-OH group.

Cyclobuxoviridine (205), isolated from *B. microphylla*,[116] contains a conjugated six-membered-ring ketone (i.r. spectrum) while the u.v. spectra show an absorption at 269 nm ($\varepsilon = 9300$). The larger bathochromic shift of this maximum suggested conjugation of a cyclopropyl methylene group with the $\alpha\beta$-unsaturated six-membered-ring system. One of the protons of the cyclopropyl methylene group is seen in the n.m.r. at 0.76 p.p.m. ($J = 5$ Hz), while the two olefinic protons are seen at 5.06 p.p.m. and 6.81 p.p.m. (AB quartet, $J = 9, 5$ Hz). Catalytic hydrogenation gives a ketone which is identical with the product obtained by Ruschig deamination[48] at C-3 of cycloprotobuxine-C.

Buxandonine (206), isolated from *B. sempervirens*,[115] is at an interesting level of demethylation of derivatives of 9β,19-cyclo-4,4,14α-trimethyl-5α-pregnane. The mass spectrum indicates a 20-dimethylamino-group, while a six-membered-ring ketone is indicated by the i.r. spectrum.

4 Alkaloids of *Pachysandra terminalis* Sieb. et Zucc.

The study of the alkaloids of *P. terminalis* is essentially the work of Japanese chemists led by Professor Kikuchi[145–156] at Kyoto. With the exception of terminaline,[150] all these alkaloids are derivatives of 3,20α-diamino-5α-pregnane. The short communications describing the establishment of the structures of most of these alkaloids have been summarised and analysed.[2]

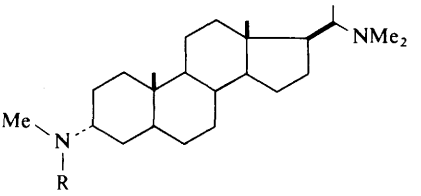
An article[145] (in Japanese) describes the methods of extraction normally used. These methods are based on a preliminary separation into weak bases and strong bases, followed by fractionation at different pH (multi-buffer method) and finally by chromatography on alumina. The Japanese article stresses the great difficulties encountered in the separation of closely related compounds. However, 27 alkaloids have been isolated in a pure form. The structures of these alkaloids are of two types:

(*A*) Derivatives of 3,20α-diamino-5α-pregnane;

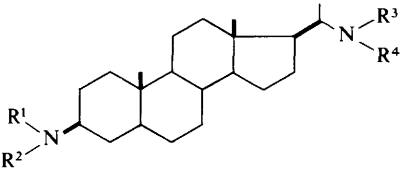
[145] M. Tomita, T. Kikuchi, S. Uyeo, T. Nishinaga, N. Yasunishi, and A. Yamamoto, *J. Pharm. Soc. Japan*, 1967, **87**, 215 (*cf. Tetrahedron Letters*, 1964, 1817).
[146] M. Tomita, S. Uyeo, and T. Kikuchi, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 193 (*cf. Tetrahedron Letters*, 1964, 1053).
[147] T. Kikuchi and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 207 (*cf. Tetrahedron Letters*, 1964, 1053 and 1817).
[148] T. Kikuchi and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 302 (*cf. Tetrahedron Letters*, 1964, 1641).
[149] T. Kikuchi, S. Uyeo, and T. Nishinaga, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 307 (*cf. Tetrahedron Letters*, 1964, 1817; 1965, 1993 and 3169).
[150] T. Kikuchi, S. Uyeo, and T. Nishinaga, *Chem. and Pharm. Bull. (Japan)*, 1965, **15**, 316 (*cf. Tetrahedron Letters*, 1965, 1993).
[151] T. Kikuchi and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 549 (*cf. Tetrahedron Letters*, 1965, 3473).
[152] T. Kikuchi and S. Uyeo, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 571 (*cf. Tetrahedron Letters*, 1965, 3487).
[153] T. Kikuchi, S. Uyeo, and T. Nishinaga, *Tetrahedron Letters*, 1966, 1749.
[154] T. Kikuchi, S. Uyeo, and T. Nishinaga, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 577.
[155] T. Kikuchi, T. Nishinaga, and Y. Yoshimura, *Tetrahedron Letters*, 1969, 1679.
[156] T. Kikuchi, T. Nishinaga, M. Inagaki, and M. Koyama, *Tetrahedron Letters*, 1968, 2077.

(*B*) Derivatives of 3,20α-diamino-5α-pregnane with oxygen at C-4. Terminaline,[150] a mono-amino-derivative, belongs to this latter type.

A. Derivatives of 3,20α-Diamino-5α-pregnane.—*Pachysamines and Epipachysamines.*[148,149] The pachysamines[148] are derivatives of 3α,20α-diamino-5α-pregnane, while the epipachysamines[149] are derivatives of 3β,20α-diamino-5α-pregnane.



Pachysamine-A, R = H
Pachysamine-B, R = $Me_2C{=}CHCO-$



Epipachysamine-A, $R^1 = R^2 = R^3 = Me$, $R^4 = Ac$
Deacetyl-epipachysamine-A, $R^4 = H$
Epipachysamine-B, $R^1 = H$, $R^2 = C_5H_4N{-}CO-$, $R^3 = R^4 = Me$
Epipachysamine-C, $R^1 = R^3 = H$, $R^2 = R^4 = Me$
Epipachysamine-D, $R^1 = H$, $R^2 = C_6H_5CO-$, $R^3 = R^4 = Me$
Epipachysamine-E, $R^1 = H$, $R^2 = Me_2C{=}CHCO-$, $R^3 = R^4 = Me$
Epipachysamine-F, $R^1 = R^2 = Me$, $R^3 = R^4 = H$

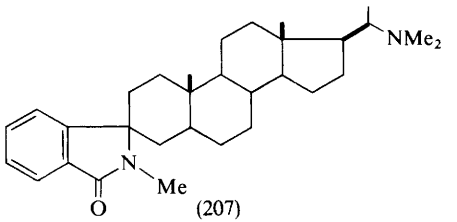
Correlations between these alkaloids have been established, and it is shown that *N*-deacetyl-epipachysamine is different from dictyophlebine, 3β-methylamino-20α-dimethylamino-5α-pregnane, isolated from *Dictyophleba lucida.*[157] Epipachysamine-C is identical with dictyodiamine from the same source. The funtudiamines-A and -B, isolated from *Funtumia latifolia,*[157] are identical with epipachysamine-F and deacetyl-epipachysamine-A.

Saracodine, an alkaloid isolated from *Sarcococca pruniformis*, and believed to be 3β-dimethylamino-20α-methylacetamido-5α-pregnane,[158] is, however, shown to be different from epipachysamine-A (see Section 5).

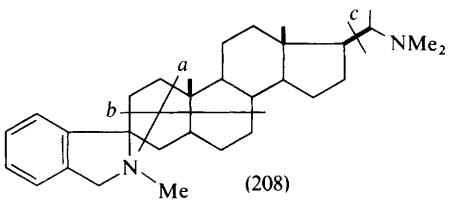
Spiropachysine (207). Spiropachysine is the principal alkaloid isolated from the leaves of *P. terminalis.*[156] It is the 'base VI' described previously.[145]

[157] Q. Khuong-Huu, X. Monseur, M. Truong-Ho, R. Kocjan, and R. Goutarel, *Bull. Soc. chim. France*, 1965, 3035.

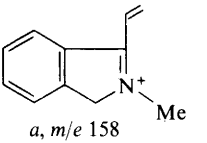
[158] A. Chatterjee, B. Das, C. P. Dutta, and K. S. Mukherjee, *Tetrahedron Letters*, 1965, 67.



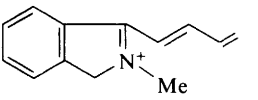
(207)



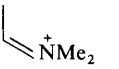
(208)



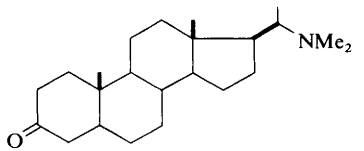
a, *m/e* 158



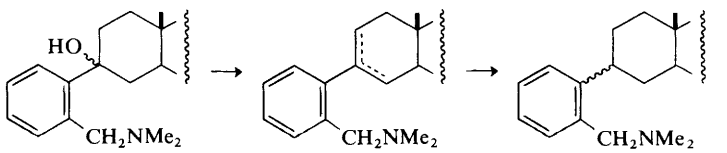
b, *m/e* 184



c, *m/e* 72



(211)



(212) (209) (210a) (210b)

The i.r. spectrum of spiropachysine (207) shows an amido-group, which is reduced by $LiAlH_4$ to give (208). The mass spectrum of (208) shows ions characteristic of 3,20-diamino-pregnanes[1,2]: ion *c*, indicating a dimethylamino-group at C-20, and ions *a* and *b* at *m/e* 158 and 184, indicating the presence of a substituent at C-3.

The absence of a double bond in the pregnane skeleton shows that spiropachysine should be hexacyclic. Since the amido-group has been shown to be at C-3,

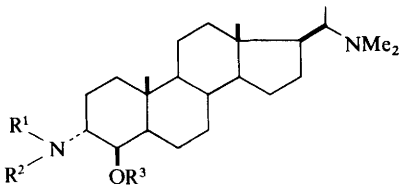
the absence of hydrogen at C-3 indicates that a five-membered-ring spiro-lactam [as in formula (207)] is present in addition to the disubstituted benzene ring.

The deoxy-compound (208) has been converted into the dimethiodide and submitted to a Hofmann degradation to give two methine bases of which one (209) is isolated by crystallisation from acetone. This derivative (209) is, in fact, a mixture of the Δ^2 and Δ^3 compounds, but catalytic hydrogenation gives a single dihydromethine (210a). On the other hand, Emde degradation of the dimethochloride of (208) (Raney nickel–NaOH) gives the second epimer (210b). The dihydromethine (210a) has been prepared from funtumafrine, 20α-dimethylamino-5α-pregnan-3-one (211).[159] Alkaloid (211) was condensed with *o*-lithiobenzyldimethylamine[160] in anhydrous ether to give the amino-alcohol (212), which was dehydrated (HCl–ethylene glycol) to (209), which, in turn, was hydrogenated to (210a).

On the basis of n.m.r., a β-configuration for the phenyl group is suggested.

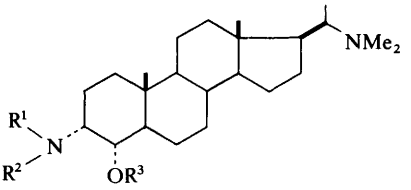
B. Derivatives of 3,20α-Diamino-5α-pregnane, oxygenated at C-4.—*Pachysandrines and Epipachysandrine-A, Terminaline.* The structures of the pachysandrines have been described earlier.[2] Further information on the establishment of these structures has been given, and correlations between the pachysandrines-A, -B, -C, and -D have been established.[146,147]

4β-Hydroxy-20α-dimethylamino-3α-methylamino-5α-pregnane was obtained by alkaline hydrolysis of pachysandrine-A, and condensed with ββ-dimethylacryloyl chloride in pyridine. Alkaline hydrolysis of the *ON*-diacyl derivative gave the *N*-acyl compound, identical with *O*-deacetylpachysandrine-B, which could be acetylated to pachysandrine-B. Mild alkaline hydrolysis of pachysandrine-D gives pachysandrine-C, which has been prepared from *O*-deacetylpachysandrine-A using the acyl migration reaction (Cornforth's acyl migration mechanism[161]).



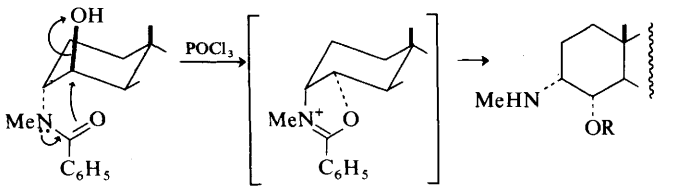
Pachysandrine-A, R^1 = Me, R^2 = C_6H_5CO, R^3 = Ac
Pachysandrine-B, R^1 = Me, R^2 = $Me_2C{=}CHCO$, R^3 = Ac

[159] M.-M. Janot, Q. Khuong-Huu, and R. Goutarel, *Compt. rend.*, 1960, **250**, 2445.
[160] F. N. Jones, R. Vaulx, and C. R. Hauser, *J. Org. Chem.*, 1963, **28**, 3461.
[161] W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, 1950, **72**, 2187.



Pachysandrine-C, R^1 = Me, R^2 = R^3 = H
Pachysandrine-D, R^1 = Me, R^2 = H, R^3 = $Me_2C{=}CHCO$

On treatment with phosphorus oxychloride, *O*-deacetylpachysandrine-A gives the benzoate (R = C_6H_5CO·) in good yield with inversion of configuration at C-4 through an intermediate oxazoline (Scheme 6).

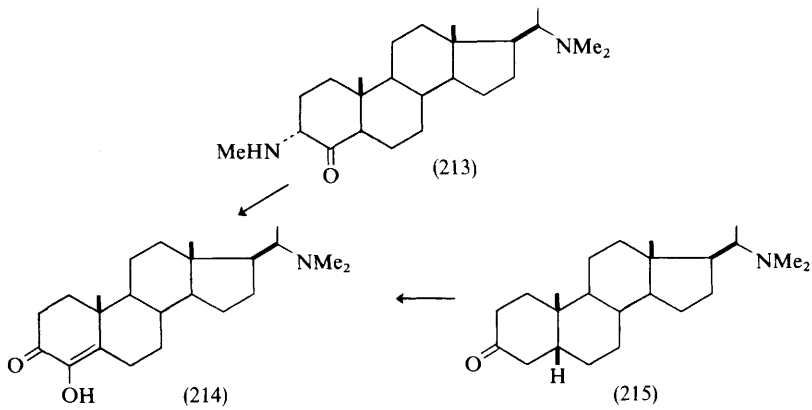


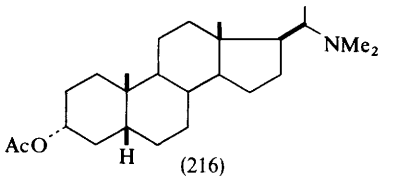
O-deacetyl pachysandrine-A

R = C_6H_5CO—
R = H, pachysandrine-C
R = $Me_2C{=}CHCO$, pachysandrine-D

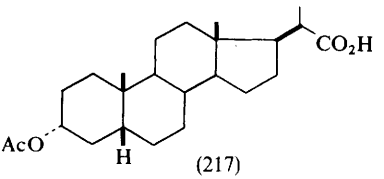
Scheme 6

The formation of the diosphenol (214) from pachysandrine-A is an interesting reaction. *ON*-Deacylpachysandrine-A was oxidised (chromic acid) to the ketone (213). Treatment of this ketone with 5% ethanolic KOH gave the diosphenol (214), which is an intermediate used in the synthesis of the pachysandrines and epipachysandrine-A.[146]





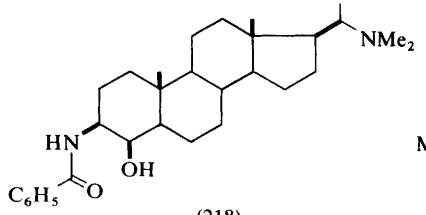
(216)



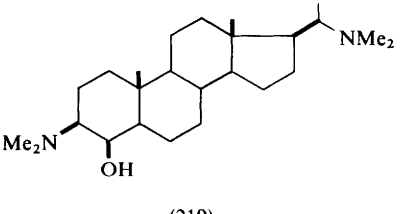
(217)

The diosphenol (214) has been prepared from 3α-bisnorcholanic acid (217), itself obtained from ergosterol. The amino-group is introduced with retention of configuration by means of the Curtius reaction and methylated to give 3α-acetoxy-20α-dimethylamino-5β-pregnane (216). After hydrolysis and oxidation with chromic acid, the ketone (215) is obtained. Aerial oxidation of (215) in the presence of potassium t-butoxide in t-butyl alcohol[162] gives (214).

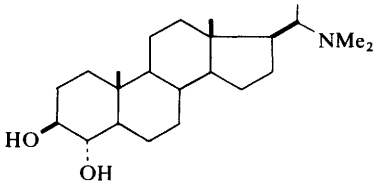
Epipachysandrine-A is a new alkaloid to which the formula (218)[153,154] has been assigned. Its synthesis from the diosphenol (214) is described below. On hydrolysis and *N*-methylation, (218) is converted into 3β,20α-bisdimethylamino-4β-hydroxy-5α-pregnane (219).



(218)



(219)



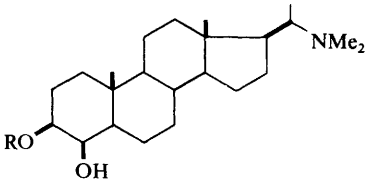
(220)

Terminaline (220) is the only monoamino-alkaloid isolated from *P. terminalis*.[150] Reduction of the diosphenol (214) by sodium in n-pentanol leads to 3β,4α-dihydroxy-20α-dimethylamino-5α-pregnane, identical with terminaline.

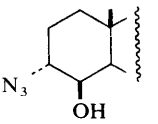
The syntheses of the pachysandrines and epipachysandrine-A have been effected starting from the diosphenol (214).[155] Reduction of (214) with sodium borohydride leads to an epimer of terminaline, 3β,4β-dihydroxy-20α-dimethylamino-5α-pregnane (221), which readily forms a mono-tosylate (222) on treatment with toluene-*p*-sulphonyl chloride in pyridine. On treatment with sodium azide in *N*-methylpyrrolidone,[163] the mono-tosylate (222) gives the azide (224) with

[162] B. Camerino, B. Pateli, and R. Sciaky, *Tetrahedron Letters*, 1961, 554.
[163] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 1962, 954.

inversion of configuration. Reduction ($LiAlH_4$) and monomethylation of (224) gives 4β-hydroxy-20α-dimethylamino-3α-methylamino-5α-pregnane (225) identical with *ON*-deacylpachysandrine-A. The synthesis of the pachysandrines-A, -B, -C, and -D starting from (225) has been described earlier.



(221), R = H
(222), R = Ts
(223), R = Ac



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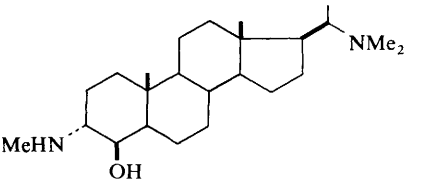

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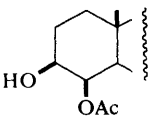

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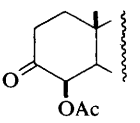
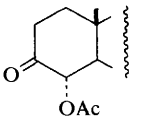
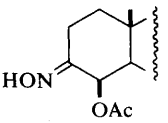


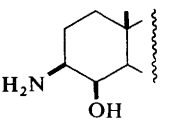
(227)



(228)



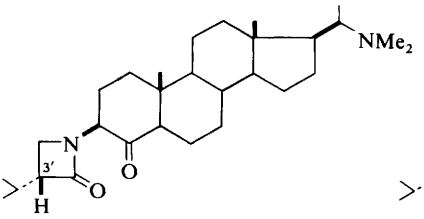
(229)



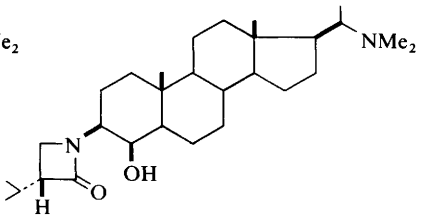
(230)

The diol (221) has been monoacetylated (Ac_2O–pyridine). The ready acyl migration of the mono-acetyl derivative (223) to (226) was effected by passage over alumina. Compound (226) was oxidised to the ketone (227) with no change in configuration at 4β. The configuration of (227) is evident from its conversion into the more stable equatorial derivative (228) on treatment with acid. The amino-group was introduced by reduction ($LiAlH_4$) of the oxime (229) to 3β-amino-20α-dimethylamino-4β-hydroxy-5α-pregnane (230). Schotten–Baumann benzoylation of (230) gave epipachysandrine-A (218).

Pachystermines-A and -B.[151] The pachystermines-A and -B present an interesting feature in possessing a β-lactam ring. They could be interconverted. A gives B on reduction with $NaBH_4$, and B gives A on oxidation with chromic acid.

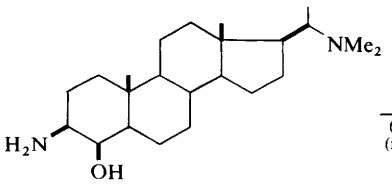


Pachystermine-A

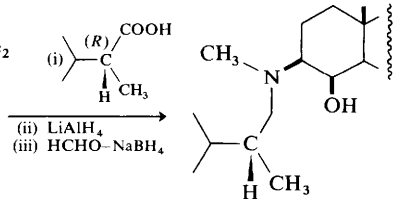


Pachystermine-B

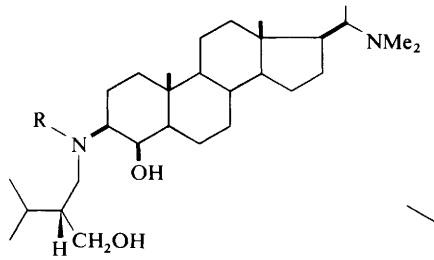
Pachystermine-A gives the diosphenol (214) on treatment with ethanolic potash. Wolff–Kishner reduction of pachystermine-A gives 20α-dimethylamino-5α-pregnane. Under the same alkaline conditions of the Wolff–Kishner reaction, pachystermine-B gives 3β-amino-20α-dimethylamino-4β-hydroxy-5α-pregnane (231), which on *N*-methylation gives the derivative (219), identical with that obtained from epipachysandrine-A.



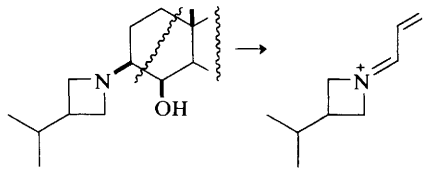
(231)



(235)



(232), R = H
(233), R = Me

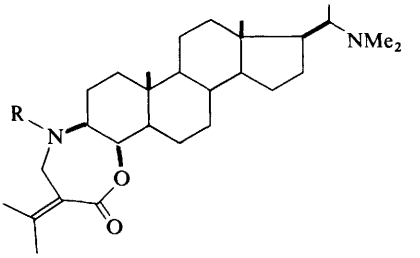


(234)

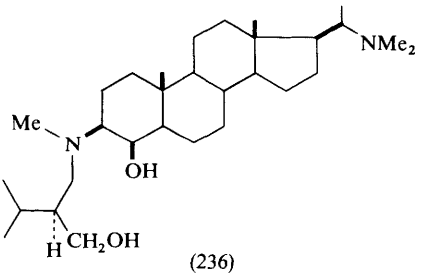
m/e 138

Reduction ($LiAlH_4$) of the pachystermines-A and -B gives the pachystermine-diol (232), which was methylated to (233). Treatment of (232) with methanesulphonyl chloride in pyridine gives the azetidine (234), characterised by an intense peak at *m/e* 138 in its mass spectrum. Under the same conditions, (233)

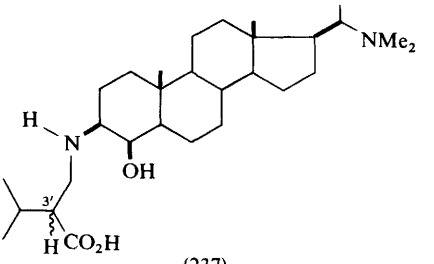
gives a mono-mesylate which is reduced by $LiAlH_4$ to the derivative (235). Condensation of 3β-amino-20α-dimethylamino-4β-hydroxy-5α-pregnane (231) with (−)(*R*)-2,3-dimethylbutyric acid[164] gives an amide which, after reduction ($LiAlH_4$) and *N*-methylation, gives (235). The configuration (3′*R*) of the pachystermines is thus demonstrated.



Pachysantermine-A, R = H



(236)



(237)

Pachysantermine-A.[152] The structure of pachysantermine-A was established by correlation with the pachystermines. Pachystermine-B is easily hydrolysed to an amino-acid (237), which is a mixture of two diastereoisomers, reduction ($LiAlH_4$) of which leads to the epimeric diols. The latter can be separated, after *N*-methyla-

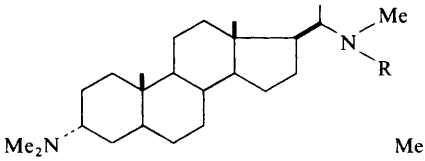
[164] K. Sakai and K. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 650.

tion, to give (233) (3′*R*) and (236) (3′*S*). Reduction ($LiAlH_4$) of dihydropachysantermine-A gives the same iso-*N*-methylpachysantermine-diol (236).

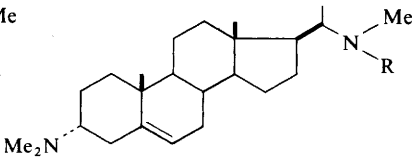
Chemical correlation has been established between the pachysandrines, epipachysandrine-A, terminaline, the pachystermines, and pachysantermine-A. Thus several plausible biogenetic relationships exist between the alkaloids of *P. terminalis.*

5 Alkaloids of *Sarcococca pruniformis* Lindl.

The structures of the alkaloids A and B, described by Kohli *et al.*,[165] have been established.[166] Alkaloid A is 3α-dimethylamino-20α-methylacetamido-5α-pregnane (238a) and alkaloid B is 3α-dimethylamino-20α-methylacetamido-pregn-5-ene (239a). The two bases have been deacetylated with lithium in ethylamine.[111] Alkaloid A (238a) gives (238b), which was methylated to (238c), identical with 3α,20α-bis(dimethylamino)-5α-pregnane.[167] Similarly, (239a) gives (239b), which may be methylated to (239c), 3α,20α-bis(dimethylamino)pregn-5-ene.[168]



(238a), R = Ac
(238b), R = H
(238c), R = CH_3



(239a), R = Ac
(239b), R = H
(239c), R = CH_3

Chatterjee *et al.*[169] have supported a 3β-dimethylamino-20α-methylacetamido-5α-pregnane structure for saracodine and a 3β-dimethylamino-20α-methylacetamidopregn-5-ene structure for saracocine. The 3α- and 3β-dimethylamino-20α-methylacetamido-5α-pregnanes and the 3α- and 3β-dimethylamino-20α-methylacetamidopregn-5-enes have, however, been synthesised by Goutarel *et al.*,[24] using the previously described stereospecific methods for introduction of amino-groups at C-3 and C-20.

Saracocine, m.p. 235—236 °C, clearly differs from 3β-dimethylamino-20α-methylacetamidopregn-5-ene, and is identical with the alkaloid B (239a) of Kohli *et al.*,[166] and with 3α-dimethylamino-20α-methylacetamidopregn-5-ene prepared by synthesis.

The melting point (190—192 °C) recorded for saracodine differs from that of 3β-dimethylamino-20α-methylacetamido-5α-pregnane (203—205 °C), and from

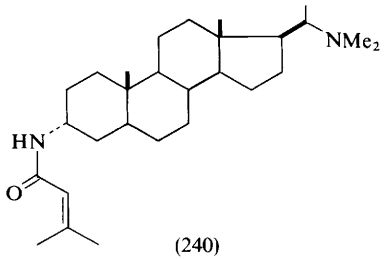
[165] J. M. Kohli, A. Zaman, and A. R. Kidwai, *Tetrahedron Letters*, 1964, 3309.
[166] J. M. Kohli, A. Zaman, and A. R. Kidwai, *Tetrahedron*, 1967, **23**, 3829.
[167] M.-M. Janot, Q. Khuong-Huu, F. Lainé, and R. Goutarel, *Bull. Soc. chim. France*, 1962, 111.
[168] V. Černy, L. Labler, and F. Šorm, *Chem. listy*, 1957, **51**, 2351.
[169] A. Chatterjee and K. S. Mukherjee, *Chem. and Ind.*, 1966, 769.

that of the alkaloid A of Kohli (245—246 °C), which is identical with that of synthetic 3α-dimethylamino-20α-methylacetamido-5α-pregnane. The abnormally low melting point recorded for saracodine is due to the fact that this alkaloid has been prepared by catalytic reduction of saracocine. It is known that the catalytic reduction of a 3α-dimethylaminopregn-5-ene gives a mixture of the 5α- and 5β-pregnane derivatives.

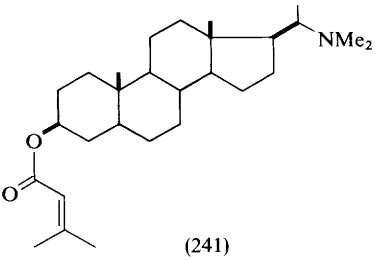
It should be added that epipachysamine-A, alkaloid of *Pachysandra terminalis*,[149] is identical with synthetic 3β-dimethylamino-20α-methylacetamido-5α-pregnane.

Kohli *et al.*[166] describe alkaloids C and D, the structures of which are not established. Chatterjee *et al.*[169] name the recently isolated alkaloids of *S. pruniformis* as alkaloids A, B, C, and D. Alkaloids A and B of Chatterjee have the structures (240) and (241) and differ from those described under the same name by Kohli. For this reason, it is proposed[24] to name the alkaloid A of Kohli (238a) as saracodine and the alkaloid B (239a) as saracocine.

An alkaloid, salignine, has been isolated[170] from *Sarcococca saligna* (synonymous with *S. pruniformis*). Later work has shown that it is identical with saracodine.[171]



(240)



(241)

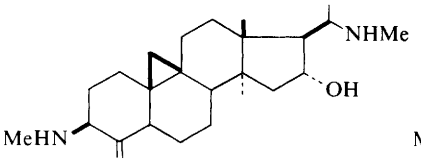
6 Biological and Biogenetic Notes

The strong interactions between certain bivalent cations and the highly ordered polynucleotides such as DNA, certain synthetic duplex homo- and heteropolymers, and s-RNA have been the subject of much current interest. With this idea in mind, it is interesting to note that the steroidal diamine cyclobuxine-D (242) was shown[172] to exert a profound effect on the stability of helical polynucleotides (DNA, s-RNA, and dAT:dAT). The effect is biphasic in the sense that at low concentrations of the agent there is stabilisation of the native conformation, while at higher concentrations there is stabilisation of the denatured conformation.

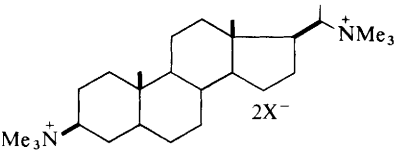
Interactions between DNA and certain steroidal diamines have been studied in comparison with Mg^{2+} and cadaverine^{2+}. These interactions are dependent

[170] M. Kiamuddin and M. E. Hacque, *Pakistan J. Sci. Ind. Res.*, 1966, **9**, 103.
[171] G. A. Miana and M. Kiamuddin, *Pakistan J. Sci. Ind. Res.*, 1969, **12**, 161.
[172] H. R. Mahler and G. Dutton, *J. Mol. Biol.*, 1964, **10**, 157.

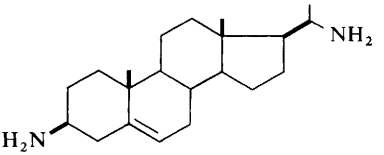
on the nature and the configuration of basic substituents in the steroid and are sensitive to minor structural changes, such as hydrogenation of a double bond. Quaternary amines, such as malouetine (243), are most effective as stabilising agents. Diprimary and disecondary but not ditertiary or diquaternary amines, in addition to stabilisation at low r (r = [ligand]/[DNA-P]), produce a destabilising effect at somewhat higher values of r. Irehdiamine-A (244) (3β,20α-diaminopregn-5-ene)[31,173,174] is particularly interesting in this respect.



(242)



(243)



(244)

The steroidal diamines, irehdiamine-A (244) (IDA) and malouetine (243) (MAL), exert an inhibiting action on the growth of bacteriophage T2 in infected cells of *Escherichia coli*. Bacteriophage-directed DNA synthesis is more sensitive to steroidal amine inhibition than RNA or protein synthesis, and it is proposed[175] that DNA is the primary target of steroidal diamine action.

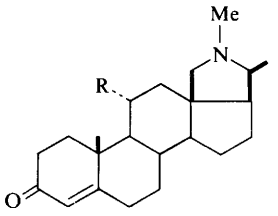
Other experiments[176–178] to distinguish between highly specific effects on particular active transport systems and more general effects on the cell membrane have shown that the primary attack of steroidal amines is not on DNA, but on the cell membrane. This results in a generalised increase in cell permeability so that small materials leak out of the cell, resulting in an inactivation of cellular permeases. The well-known antibiotic activity not only of steroidal diamines, but also of steroidal mono-amines, can be explained by such an effect on the permeability of the cells.

The toxicity of steroidal amines is such that it is sometimes difficult to perform on them the microbiological reactions normally done with other steroids. How-

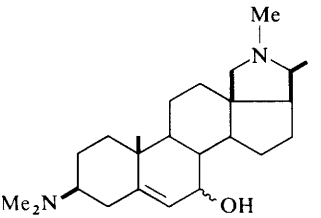
[173] H. R. Mahler, R. Goutarel, Q. Khuong-Huu, and M. Truong-Ho, *Biochemistry*, 1966, **5**, 2177.
[174] H. R. Mahler, G. Green, R. Goutarel, and Q. Khuong-Huu, *Biochemistry*, 1968, **7**, 1568.
[175] H. R. Mahler and M. B. Baylor, *Proc. Nat. Acad. Sci. U.S.A.*, 1967, **58**, 256.
[176] S. Silver and E. Levine, *J. Bacteriol.*, 1968, **96**, 338.
[177] S. Silver and E. Levine, *Biochem. Biophys. Res. Comm.*, 1968, **31**, 743.
[178] S. Silver, L. Wendt, P. Bhattacharyya, and R. S. Beauchamp, *Ann. N.Y. Acad. Sci.*, 'Metabolism and Biological Functions of Polyamines,' April 9—19, 1970.

ever, microbiological hydroxylation of funtumine and funtumidine has been effected using *Aspergillus ochraceus* NRRL 405 in aerobic fermentation. The reaction gives the 11- and 12-hydroxy-derivatives.[179] 12β-Hydroxy-funtumine is identical with bokitamine (20).[12]

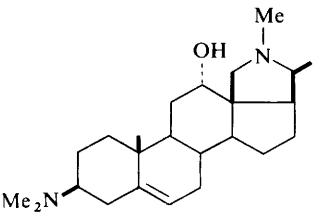
Conessine (1) is converted by *Gloesporium cyclaminis* or *Hypomyces haematococcus* into conan-4-en-3-one (245, R = H),[180] identical with latifolinine of *Funtumia latifolia*.[1,2]



(245)



(246)



(247)

Incubation of conessine with *Stachybothrys parvispora* yielded conan-4-en-3-one (245, R = H) and 11α-hydroxy-conan-4-en-3-one (245, R = OH). Fermentation with *Gloesporium fructigenum* resulted in a mixture (246) of 7α-hydroxyconessine and 7β-hydroxyconessine, along with 11α-hydroxyconessine.[181] The two epimers (246) have also been obtained by incubation with *Aspergillus ochraceus*[182] and *Cunninghamella echinulata*.[183] Incubation of conessine with *Botryodiplodia theobromae* gave 9α-hydroxyconessine and 12α-hydroxyconessine (247), which has been converted into its 12β-epimer, holarrhenine, an alkaloid of *Holarrhena floribunda*.[184] *Penicillium atramentosum* reduces the 3-keto-group

[179] G. Greenspan, R. Rees, L. L. Smith, and H. E. Alburn, *J. Org. Chem.*, 1965, **30**, 4215.
[180] J. de Flines, A. F. Marx, W. F. van der Waard, and D. van der Sidje, *Tetrahedron Letters*, 1962, 1257.
[181] A. F. Marx, H. C. Beck, W. F. van der Waard, and J. de Flines, *Steroids*, 1966, **8**, 421.
[182] S. M. Kupchan, C. J. Sih, S. Kubota, and A. M. Rahim, *Tetrahedron Letters*, 1963, 1767.
[183] E. L. Patterson, W. W. Andres, and R. E. Hartman, *Experientia*, 1964, **20**, 256.
[184] A. F. Marx, H. C. Beck, W. F. van der Waard, and J. de Flines, *Steroids*, 1966, **8**, 391.

of 3-oxo-*N*-demethyl-conan-20(*N*)-ene to 3β-hydroxy[185] without reducing the imino-group.

The origin of the steroidal alkaloids of the Apocynaceae and some of the Buxaceae (*Sarcococca* and *Pachysandra*) appears to be linked with the biogenesis in these plants of steroidal derivatives of pregnanes, pregnenolone in particular. The *Buxus* alkaloids appear to be derived from 4,4,14α-trimethyl-9β,19-cyclo-5α-pregnanes.

Progesterone and pregnenolone have been isolated from the leaves of *Holarrhena floribunda*[7] and it has been shown that pregnenolone is the precursor of holaphyllamine (3β-aminopregn-5-en-20-one) and holamine (3α-aminopregn-5-en-20-one)[186] as well as of conessine.[187] It is known that progesterone takes part in the biosynthesis of cardenolides,[188,189] and it appears reasonable to suppose that it is involved in the same way in the biosynthesis of the new amino-glycocardenolides found in the leaves of Asiatic *Holarrhena*.

It appears that in plants cycloartenol plays a rôle equivalent to that of lanosterol in animal tissues,[190—194] and it seems reasonable to derive directly from cycloartenol (248) the *Buxus* alkaloids, of which the prototype is represented by the cycloprotobuxines (252). The study of the unsaponifiable fraction of the oil of the seeds of *Funtumia elastica*, *Funtumia latifolia*,[195] and *Holarrhena floribunda*[196] has shown the existence in these genera of a remarkable sequence of tetracyclic triterpenes and sterols containing a side-chain unbranched at C-24 and ending in an isopropylidene group. The interconversion of these compounds takes place by demethylation and isomerisation of the unsaturation of the carbon skeleton: 9β,19-cyclo $\rightarrow \Delta^{8(9)} \rightarrow \Delta^{7} \rightarrow \Delta^{5}$, cycloartenol (248), 31-norlanosterol (249), 24-dehydrolophenol (250), desmosterol (251). On the other hand, the alkaloids isolated from the seeds of *Funtumia* belong to the irehdiamine group (253), while those from the seeds of *Holarrhena* are holarrhimine (254),[197] conkurchine (255), and conarrhimine (256, $R^1 = R^2 = R^3 = H$) and its various *N*-methylated derivatives.[196] An interesting biogenetic hypothesis would be to derive the irehdiamines (pregn-5-enes) from desmosterol (the presence of the Δ^{24} double-bond being perhaps necessary for the cleavage of the side-chain);

[185] T. Nguyen-Dang, M. Fonquernie, and M.-M. Janot, *Ann. pharm. franç.*, 1966, **24**, 523.
[186] R. D. Bennett and E. Heftmann, *Phytochemistry*, 1965, **4**, 873.
[187] R. Tschesche and H. Hulpke, *Z. Naturforsch.*, 1968, **23b**, 2.
[188] E. Caspi and D. O. Lewis, *Science*, 1967, **156**, 519.
[189] R. D. Bennett, H. H. Sauer, and E. Heftmann, *Phytochemistry*, 1968, **7**, 41.
[190] P. Benveniste, L. Hirth, and G. Ourisson, *Phytochemistry*, 1966, **5**, 45.
[191] J. D. Ehrhardt, L. Hirth, and G. Ourisson, *Compt. rend.*, 1965, **260**, 5931.
[192] J. D. Ehrhardt, L. Hirth, and G. Ourisson, *Phytochemistry*, 1967, **6**, 815.
[193] L. J. Goad and T. Goodwin, *Biochemistry*, 1966, **99**, 735.
[194] P. Ponsinet and G. Ourisson, *Bull. Soc. chim. France*, 1965, 3682.
[195] G. Charles, T. Njimi, G. Ourisson, J. D. Ehrhardt, C. Conreur, A. Cavé, and R. Goutarel, *Compt. rend.*, 1969, **268**, *C*, 2105.
[196] C. Conreur, M. Lebœuf, A. Cavé, and R. Goutarel, *Ann. pharm. franç.*, 1970, **28**, 649.
[197] H. Favre, R. D. Haworth, J. McKenna, R. G. Powell, and G. H. Whitfield, *J. Chem. Soc.*, 1953, 1115.

HO
(248)
(249)
(250)
(251)
R^1R^2N
NR^3R^4
(252) (*Buxus*
(253) (*Funtumia*)
H_2N
NH_2
$HO-CH_2$
(254) (*Holarrhena*)
(255)
(256)
R^3
N

the alkaloids of the conanine group would then be derived from the irehdiamines by oxidation of the methyl group at C-13 (holarrhimine → conkurchine → conarrhimine). The *Funtumia* genus of the Echitoideae sub-family in the Apocynaceae can be considered as a natural 'mutant' of the *Holarrhena* genus of the Plumieroideae sub-family. The seeds of both genera contain the entirety of all the compounds at different stages in the biogenesis of conarrhimine and conessine from cycloartenol.

I am grateful to Drs. F. X. Jarreau, F. Khuong-Huu, Q. Khuong-Huu, P. Longevialle, X. Lusinchi, and C. Monneret for their part in the preparation of this report, and thank Dr. G. P. Wannigama for translating the French manuscript.

18
Peptide Alkaloids

BY E. W. WARNHOFF

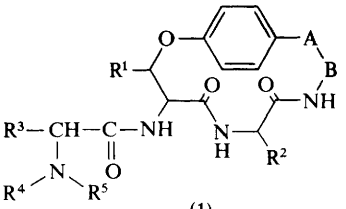
Although the peptide alkaloids were first recognised as a new type of plant base only about six years ago, this expanding group now contains twenty-seven members of known structure and has been the subject of two very recent reviews.[1,2] The fact that these basic compounds are composed largely of amino-acids joined by amide linkages suggested the name 'peptide alkaloids,'[3] and their relatively small size, plant origin, and non-amino-acid component all make this designation preferable to the alternative description as 'basic peptides.' The term is presently understood to include those bases containing three or four simple amino-acids plus a modified hydroxyphenylethylamine unit.* These alkaloids have so far been found in small amounts (0.02—0.9%) in thirteen plants of six families, mainly the Rhamnaceae.

Early studies[4] on one of the plants, *Ceanothus americanus*, showed the alkaloid fraction to be a complex mixture of closely related compounds, as has since been found to be true for most of the other plants examined. Little real progress in the chemistry of these compounds was possible until the recent development of the more refined separation and analytical techniques of thin-layer chromatography, n.m.r., and organic mass spectroscopy. The structures of the first few bases (pandamine,[5] zizyphine,[6] ceanothine-B,[7] scutianine,[8] and the adouétines[9]) were determined by a combination of chemical degradation and applied spectroscopy. More recently, automatic amino-acid and mass spectroscopic analysis of these

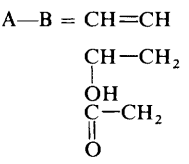
[1] M. Païs and F.-X. Jarreau, *Advances in Peptide Chemistry*, 1971, to appear.
[2] E. W. Warnhoff, *Fortschr. Chem. org. Naturstoffe*, 1970, **28**, to appear.
[3] M. Païs, X. Monseur, X. Lusinchi, and R. Goutarel, *Bull. Soc. chim. France*, 1964, 817.
[4] H. M. Gordin, *Pharm. Rev.*, 1900, **18**, 266; A. H. Clark, *Amer. J. Pharm.*, 1926, **98**, 147; 1928, **100**, 240; A. Bertho and W. S. Liang, *Arch. Pharm.*, 1933, **271**, 273; C. W. Roscoe and N. A. Hall, *J. Amer. Pharm. Assoc., Sci. Ed.*, 1960, **49**, 108.
[5] M. Païs, F.-X. Jarreau, X. Lusinchi, and R. Goutarel, *Ann. Chim. (France)*, 1966, **1**, 83.
[6] E. Zbiral, E. L. Ménard, and J. M. Müller, *Helv. Chim. Acta*, 1965, **48**, 404.
[7] E. W. Warnhoff, J. C. N. Ma, and P. Reynolds-Warnhoff, *J. Amer. Chem. Soc.*, 1965, **87**, 4198; F. K. Klein and H. Rapoport, *ibid.*, 1968, **90**, 3576; R. E. Servis and A. I. Kosak, *ibid.*, 1968, **90**, 4179.
[8] R. Tschesche, R. Welters, and H.-W. Fehlhaber, *Chem. Ber.*, 1967, **100**, 323.
[9] M. Païs, J. Marchand, F.-X. Jarreau, and R. Goutarel, *Bull. Soc. chim. France*, 1968, 1145.

* The term might be extended to include certain other alkaloids, likely of amino-acid origin, having two amide groups; these compounds are mentioned at the end of this Report.

alkaloids has been developed to the point where the structures of new bases can often be deduced from these measurements alone.[10,11]

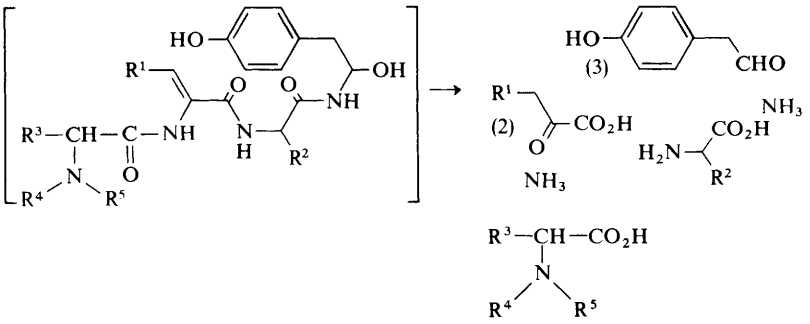


(1)



R^1, R^2, R^3 = amino-acid alkyl residues

R^4, R^5 = H, Me, or an amino-acid



All but three of the twenty-eight alkaloids (for a complete list see Table 1) conform to the general formula (1), having a peptide macrocycle, composed of an amino-acid, a β-hydroxyamino-acid, and a modified tyramine unit, to which is attached *via* an amide bond one or two more amino-acids. The A—B portion is a two-carbon unit of varying oxidation state, usually a double bond (22 of 25 compounds). The amino-acids encountered so far are leucine, isoleucine, valine, phenylalanine, proline, tryptophan, and their *N*-methylated and β-hydroxylated derivatives. The compounds are therefore monobasic (exception: lasiodine-A) and, because of the α-carboxamido-group, are relatively weak, with pK_a's ranging from ~5—6.5 in the methylcellosolve–water system. The unique feature of an enamide group within a macrocyclic ring confers some interesting physical and chemical properties which have been discovered during structural work on these alkaloids.

The enamide function is the point most susceptible to attack during acidic hydrolysis of a peptide alkaloid and is responsible for the pink to purple colours

[10] H.-W. Fehlhaber, *Z. analyt. Chem.*, 1968, **235**, 91.
[11] R. Tschesche, E. Frohberg, and H.-W. Fehlhaber, *Tetrahedron Letters*, 1968, 1311.

Table 1 *Peptide alkaloids*

Alkaloid	*Formula*[a]
Adouétine-X[b]	$Me_2Leu\rightarrow 3Hyleu\rightarrow Ile\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Adouétine-Y[b]	$Me_2Phe\rightarrow 3Hyphe\rightarrow Ile\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Adouétine-Y'[b]	$Me_2Phe\rightarrow 3Hyleu\rightarrow Ile\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Adouétine-Z[b]	$Me_2Phe\rightarrow Pro\rightarrow 3Hyphe\rightarrow Phe\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Americine[c]	$Me_2Val\rightarrow 3Hyleu\rightarrow Trp\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Aralionine[d]	$Me_2Ile\rightarrow 3Hyphe\rightarrow NH{\cdot}\underset{\displaystyle O{=}CC_6H_5}{\underset{\vert}{CH}}{\cdot}CO{\cdot}NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Canthiumine[e]	$Me_2Phe\rightarrow 3Hyphe\rightarrow Pro\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Ceanothine-A[f]	$MePhe\rightarrow 3Hyleu\rightarrow \left\{\begin{matrix}Leu\\Ile\end{matrix}\right\}\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Ceanothine-B[g]	$MePro\rightarrow 3Hyleu\rightarrow Phe\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Ceanothine-C[h]	$MePro\rightarrow 3Hyleu\rightarrow \left\{\begin{matrix}Leu\\Ile\end{matrix}\right\}\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Ceanothine-D[h]	$MePro\rightarrow 3Hyile\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Ceanothine-E[h]	$Me_2Phe\rightarrow 3Hyphe\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Franganine[i]	$Me_2Leu\rightarrow 3Hyleu\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Frangufoline[i]	$Me_2Phe\rightarrow 3Hyleu\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Frangulanine[j]	$Me_2Ile\rightarrow 3Hyleu\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Hymenocardine[k]	$Me_2Ile\rightarrow Val\rightarrow 3Hyval\rightarrow Trp\rightarrow NHCH_2{\cdot}C(=O){\cdot}C_6H_4{\cdot}O\text{-}p$
Integerrenine[l]	$Me_2Ile\rightarrow 3Hyphe\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Integerressine[l]	$Me_2Val\rightarrow 3Hyphe\rightarrow Phe\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Integerrine[m]	$Me_2Val\rightarrow 3Hyphe\rightarrow Trp\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Lasiodine-A[n]	Formula 8
Lasiodine-B[n]	$MePhe\rightarrow Pro\rightarrow 3Hyleu\rightarrow Leu\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Myrianthine-A[o]	$Me_2Leu\rightarrow 3Hyphe\rightarrow Ile\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Myrianthine-C[o]	$Me_2Leu\rightarrow 3Hyleu\rightarrow Val\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Pandamine[p]	$Me_2Ile\rightarrow 3Hyleu\rightarrow Phe\rightarrow NHCH_2CH(OH){\cdot}C_6H_4{\cdot}O\text{-}p$
Pandaminine[p]	$Me_2Val\rightarrow 3Hyleu\rightarrow Phe\rightarrow NHCH_2CH(OH){\cdot}C_6H_4{\cdot}O\text{-}p$
Scutianine[q]	$Me_2Phe\rightarrow Pro\rightarrow 3Hyleu\rightarrow Phe\rightarrow NHCH{=}CH{\cdot}C_6H_4{\cdot}O\text{-}p$
Zizyphine[r]	Formula 7
Zizyphinine[r]	Structure not known; perhaps zizyphine with Val in place of an Ile moiety.

[a] Although it is not shown in these abbreviated structural formulae, the ether bond linking the *p*-position of the aromatic ring to the β-position of the β-hydroxylated amino-acid is understood to be present. [b] Ref. 9. [c] Ref. 12. [d] Ref. 15. [e] G. Boulvin, R. Ottinger, M. Païs, and G. Chiurdoglu, *Bull. Soc. chim. belges*, 1969, **78**, 583. [f] Ref. 2. [g] Ref. 7. [h] R. E. Servis, A. I. Kosak, R. Tschesche, E. Frohberg, and H.-W. Fehlhaber, *J. Amer. Chem. Soc.*, 1969, **91**, 5619. [i] R. Tschesche and H. Last, *Tetrahedron Letters*, 1968, 2993. [j] Ref. 14. [k] Ref. 18. [l] Ref. 16. [m] Ref. 11. [n] Ref. 17. [o] J. Marchand, X. Monseur, and M. Païs, *Ann. pharm. franç.*, 1969, **27**, 771. [p] Ref. 5. [q] Ref. 8. [r] Ref. 6.

observed. The products are simple amino-acids, a volatile α-keto-acid (2) originating from the β-hydroxyamino-acid, and ammonia from both the enamide and β-hydroxyamino-acid portions. The expected *p*-hydroxyphenylacetaldehyde (3) is presumably lost by condensation in the dark-coloured insoluble material formed. If the hydrolysis is carried out instead on the hydrogenated alkaloid (1; CH_2CH_2 for A—B), in which the enamide group has been saturated, not only

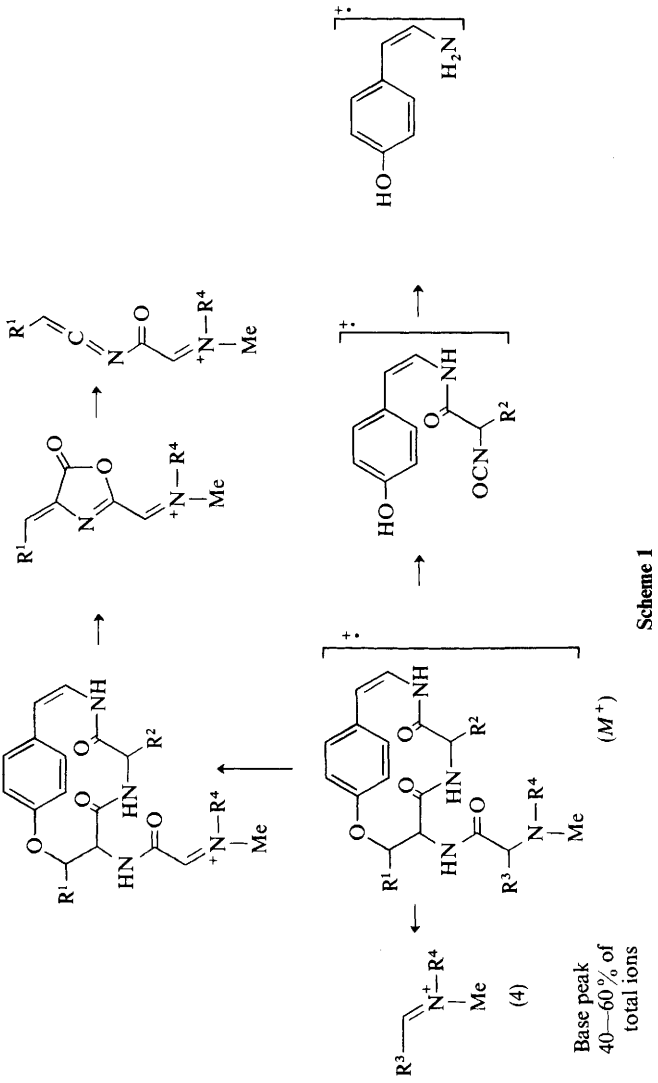
are no colours developed and no insoluble coloured material formed, but tyramine is now one of the products and the yield of ammonia is decreased.[8,12] If the hydrolysis of the hydrogenated alkaloid is not carried to completion, the macrocyclic portion free of the appended amino-acid(s) can be isolated.[7,8] For these reasons hydrolysis of the hydrogenated alkaloids has been more useful in structural work. On basic hydrolysis of these alkaloids, the enamide function also appears to be the initial point of attack since refluxing methanolic hydroxide removes the enamide u.v. absorption (~260 nm) of ceanothine-B without fragmenting the molecule.[13]

During acidic and, particularly, basic hydrolysis, side-products arise from the β-hydroxyamino-acid unit. Thus, a β-aryloxyleucine portion after elimination of the aryloxy-group can give rise to leucine[5,8,12,14] by transamination and to glycine[8] by conjugate addition of water and retroaldol cleavage. On acidic hydrolysis, a β-aryloxyphenylalanine portion gives β-phenylnaphthalene,[15,16] presumably from self-condensation of some species equivalent to phenylacetaldehyde.

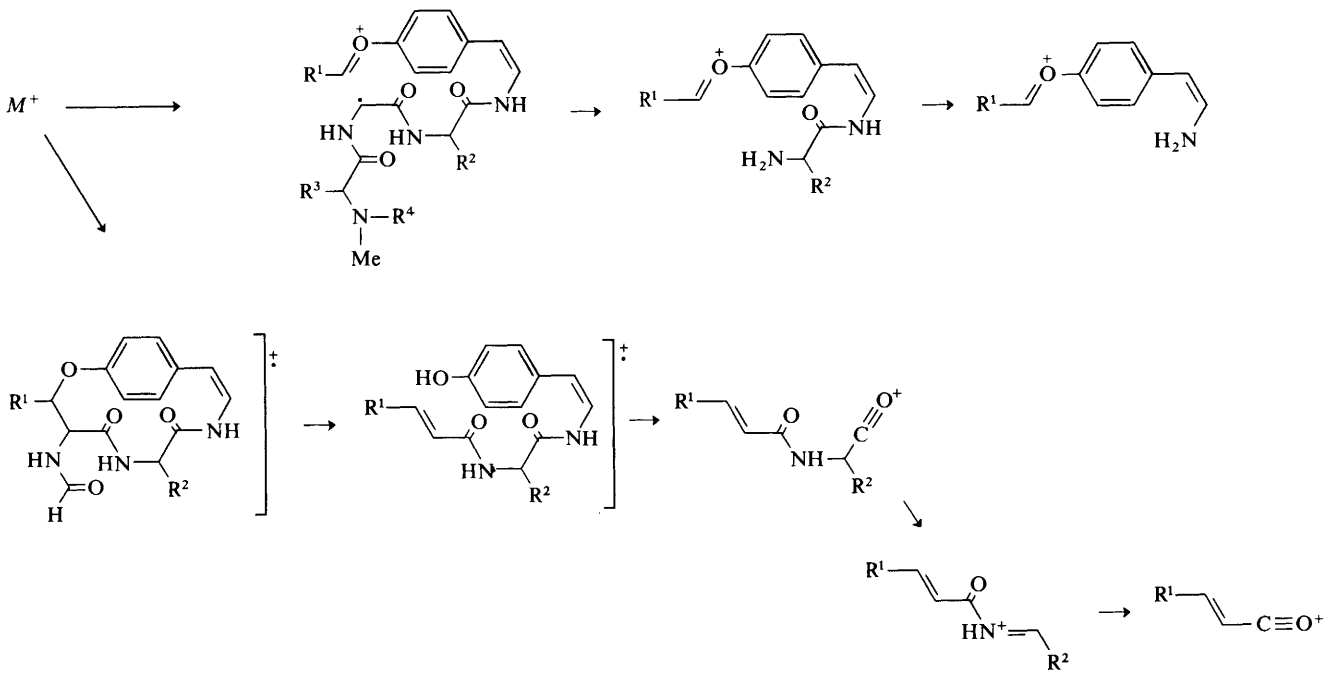
For those alkaloids whose quantity has been insufficient to permit isolation of the hydroxyphenylethylamine, the orientation of the substituents on the aromatic ring (not always obvious from the n.m.r. spectrum) has been determined by ozonolysis of the alkaloid,[8] or else by a combined paper chromatography–u.v. absorption method[15] applied to the hydrolysate of the dihydroalkaloid. The styrylamide double bond of these alkaloids is rapidly broken by ozone, and the u.v. spectrum of the resulting *p*-aryloxybenzaldehyde (λ_{max} 275 nm) is readily distinguished from the *o*- and *m*-isomers (λ_{max} 253 nm).

Reconstitution of the alkaloid structure from the identified fragments can be done by inspection if only *two* amino-acids (excluding artifacts) are produced on hydrolysis, because the terminal group attached to the macrocycle contains a partially or completely methylated basic nitrogen atom. If *three* amino-acids are found, then which of the two non-*N*-methylated ones is part of the macrocycle and which is outside can be determined most simply from the mass spectrum. In most cases the application of high-resolution mass spectroscopy to peptide alkaloids permits the determination of the complete structure without hydrolytic studies because of the characteristic peptide decomposition pattern. The breakdown sequence with proposed ion structures is given in Scheme 1.[10] The terminal unit of an alkaloid bearing the amino function gives by far the most intense peak in the mass spectrum corresponding to (4). The only points of ambiguity are the distinction between leucine and isoleucine and the substitution pattern on the aryloxy ring. Leucine and isoleucine in the N_{basic} terminal amino-acid can be distinguished by the secondary decomposition of R^3 in the base-peak ion: the isoleucyl ion (5) loses an ethyl radical, while the leucyl ion (6) loses propene.

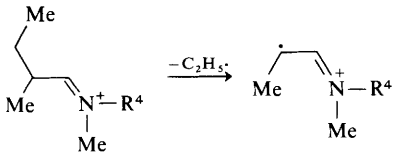
[12] F. K. Klein and H. Rapoport, *J. Amer. Chem. Soc.*, 1968, **90**, 2398.
[13] E. W. Warnhoff and P. Reynolds-Warnhoff, unpublished observation.
[14] R. Tschesche, H. Last, and H.-W. Fehlhaber, *Chem. Ber.*, 1967, **100**, 3937.
[15] R. Tschesche, L. Behrendt, and H.-W. Fehlhaber, *Chem. Ber.*, 1969, **102**, 50.
[16] R. Tschesche, J. Rheingans, H.-W. Fehlhaber, and G. Legler, *Chem. Ber.*, 1967, **100**, 3924.



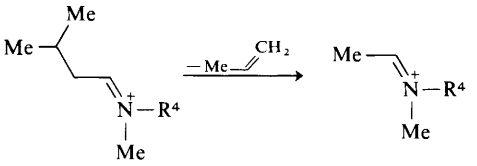
Scheme 1



Scheme 1 (contd.)

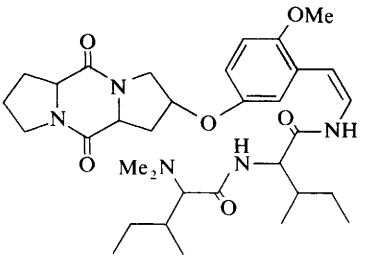


(5)



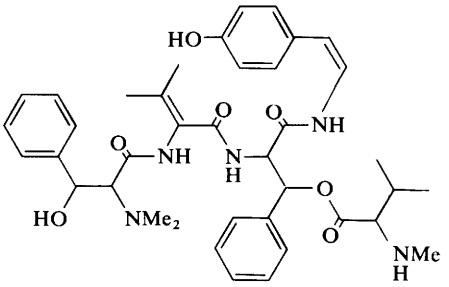
(6)

In the u.v. spectra of peptide alkaloids the most interesting feature is the difference in the aryloxyenamide chromophore, depending on whether it is part of a macrocycle or not. If not, there appears a long-wavelength maximum due to the entire chromophore, as observed in zizyphine (7)[6] (λ_{max} 267 and 319 nm) and lasiodine-A (8)[17] (λ_{max} 281 nm). Inclusion of the group within a fourteen-membered macrocyclic ring reduces conjugation, and no absorption maxima are present above 200 nm. In fact, a molecular model shows that in the macrocycle the *p*-orbitals of the aryloxy and enamide chromophores cannot overlap to any extent, and each group must absorb independently. In confirmation, the summation of model enamide and *p*-alkoxybenzene chromophores is almost identical with the u.v. spectrum of typical alkaloids.[2] Conversely, if the u.v. spectrum of a dihydro macrocyclic enamide alkaloid is subtracted from that of the alkaloid, there remains the simple enamide chromophore.[2] As another example of the effect of the macrocyclic ring on conjugation, even the more flexible ketone (9) derived from pandamine[5] shows evidence of only partial conjugation (λ_{max} 266 nm, ε 7400) with the aromatic ring when compared with anisaldehyde (λ_{max} 273 nm, ε 17 300).

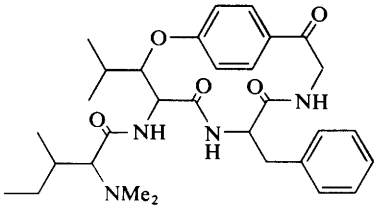


(7)

[17] J. Marchand, M. Païs, X. Monseur, and F.-X. Jarreau, *Tetrahedron*, 1969, **25**, 937.

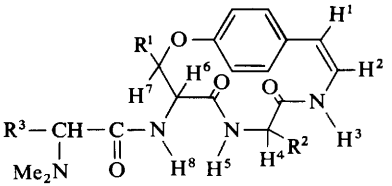


(8)



(9)

In the n.m.r. spectra of the macrocyclic alkaloids (10) there are a number of points of interest which depend on stereochemistry. The chemical shift of the two protons H-1 and H-2 of the enamide group is very dependent upon pH. In deuteriochloroform both are near δ 6.4, but in acetic acid H-1 appears $\sim\delta$ 6.8



(10)

and H-2 at $\sim\delta$ 6.0. The H-7 proton on the carbon atom bearing the aryloxy-group appears by itself in the region δ^{CDCl_3} ~4.8—5.25, apparently in the de-shielding zone of the aromatic ring because in non-macrocyclic analogues this proton is at δ^{CDCl_3} 4.3.[5] Protons H-3, H-4, H-5, and H-6 on the macrocyclic ring are in the shielding zone of the aryloxy ring. Methine protons H-4 and H-6 on the α-carbon atoms of the amino-acids in the ring appear at δ 4.0—5.0, upfield about 0.5—1.0 p.p.m. from their usual position in linear peptides. Of the three amide

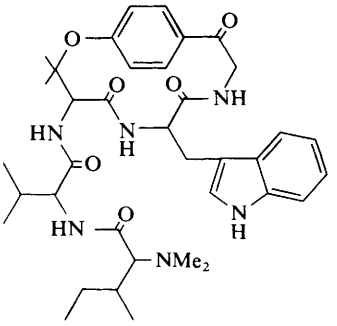
NH protons, H-3 and H-5 experience the shielding effect of the aromatic ring-current and appear in the vicinity of δ^{CDCl_3} 6.4 overlapping the enamide hydrogens H-1 and H-2, while H-8 is less affected and appears in the expected position near δ^{CDCl_3} 7.7. Two of these NH protons (H-5 and H-8) are exchanged immediately on contact with deuterium oxide, but the third (H-3) is not noticeably affected even after an hour at 37 °C. Rapid exchange of the enamide proton H-3 occurs only on addition of acid.[13] When R^1 is isopropyl the two methyl doublets are separated ($\Delta\delta$ 0.3—0.4), presumably because of differing anisotropic effects.[7,8,12] When R^1 is phenyl the two *N*-methyl groups on the terminal amino-acid of some of the alkaloids experience different degrees of anisotropic shielding and appear as well-separated ($\Delta\delta$ 0.4—0.7 p.p.m.) signals.[9,16]

The stereochemistry of the peptide alkaloids is a simple matter. The amino-acid components have been found to belong to the L-series except for D-*threo*-*β*-phenylserine in lasiodine-A. This stereochemistry is reflected in the moderately negative optical rotations ($[\alpha]_D$ *ca.* −80 to −150°) of the hydrogenated bases. On the other hand, the alkaloids themselves have much larger negative rotations ($[\alpha]_D$ *ca.* −200 to −400°) due to the inherently dissymmetric styrene chromophore enclosed within the peptide macrocycle. The chirality of this chromophore is apparently the same in all of the macrocyclic enamide alkaloids. Those *β*-hydroxy-amino-acids whose configuration has been examined have been found to belong to the *threo*-series. In all of the alkaloids (macrocyclic or not) containing the styrylamide group, the coupling constants of the olefinic protons ($J_{H^1—H^2}$ 7.5—11 Hz) argue for the *cis* configuration of the double bond, and indeed only a *cis* double bond can be accommodated within the ring.

The few alkaloids which do not have the macrocyclic enamide structure (1) are still related to it. Pandamine (1, CHOH·CH_2 for A—B), pandaminine (1; CHOH·CH_2 for A—B), and hymenocardine (11)[18] are merely variants with different hydration or oxidation states of A—B. Lasiodine-A (8)[17] is non-macrocyclic but has both the free phenolic hydroxy-group and the *αβ*-unsaturated amide that would result from opening (or possibly be required for closing) a macrocyclic ring. Opening of the macrocyclic ring by *β*-elimination during alkaline hydrolysis has been observed with hymenocardine (11),[18] in which special case the phenolate is a better leaving-group because of the benzylic ketone. Zizyphine (7),[6] the only alkaloid in which the aromatic ring has the homogentisic acid orientation of substituents, might be regarded as a frustrated potential *m*-bridged macrocycle.

In the biogenesis of the peptide alkaloids the major point of interest is the way in which the macrocycle is closed. There is as yet no evidence, but one suspects that one of the bonds to the ether oxygen is formed last. Since the precursor of the tyramine unit in these bases is doubtless *p*-hydroxyphenylalanine, the ring might be closed by conjugate addition of the phenolic hydroxy-group to an unsaturated amide of the lasiodine-A (8) type, or perhaps by conjugate addition of an oxidised *p*-hydroxyphenylalanine unit to an unsaturated amide (12). The

[18] M. Païs, J. Marchand, G. Ratle, and F.-X. Jarreau, *Bull. Soc. chim. France*, 1968, 2979.



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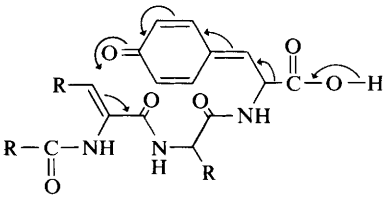


(12)

latter path or some variant of it would readily explain the presence of the enamide double bond.

Although many of the plants in which peptide alkaloids occur have been used in folk medicine, the few pharmacological studies[19] of the alkaloids so far made have not revealed any interesting properties; the alkaloids are not particularly toxic.

Finally, there are a few alkaloids having two amide groups, whose structures are not so closely related to simple α-amino-acid peptides. However, their components obviously were derived from α-amino-acids at some stage. Six of these[20] are related to lunarine (13), whose stereostructure has been determined by *X*-ray analysis.[21] Its biogenesis would involve oxidative coupling of two *p*-hydroxyphenylalanine units and amide formation with spermidine, itself of amino-acid origin. The alkaloid undergoes an interesting aromatisation rearrangement to (14) on alkali fusion.[2,22] Homaline, a recently found alkaloid,[23] also bears a

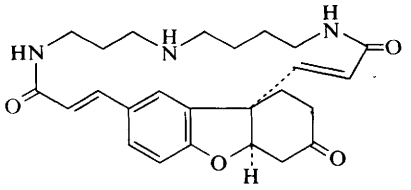
[19] O. Blanpin, M. Païs, and M. A. Quevauviller, *Ann. pharm. franç.*, 1963, **21**, 147; A. A. Manian, Ph.D. Thesis, Purdue University, 1954; C. W. Roscoe and N. A. Hall, *J. Amer. Pharm. Assoc., Sci. Ed.*, 1960, **49**, 108.

[20] C. Poupat, B. Rodriguez, H.-P. Husson, P. Potier, and M.-M. Janot, *Compt. rend.*, 1969, **269**, *C*, 335; M.-M. Janot and J. Le Men, *Bull. Soc. chim. France*, 1956, 1840; P. Potier, J. Le Men, and M.-M. Janot, *ibid.*, 1959, 201.

[21] J. A. D. Jeffreys and G. Ferguson, *J. Chem. Soc.* (*B*), 1970, 826; C. Tamura and G. A. Sim, *ibid.*, 1970, 991.

[22] P. Bladon, M. Chaigneau, M.-M. Janot, J. Le Men, P. Potier, and A. Melera, *Tetrahedron Letters*, 1961, 321.

[23] M. Païs, R. Ratle, R. Sarfati, and F.-X. Jarreau, *Compt. rend.*, 1968, **266**, *C*, 37; 1968, **267**, *C*, 82.



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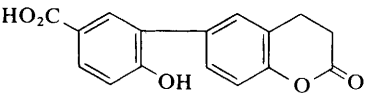

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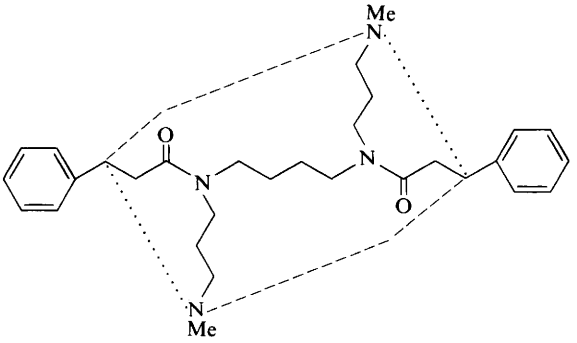


(15)

distant biogenetic relation to lunarine in that it is probably derived from two molecules of phenylalanine and one of spermine. Which of the two possible ring structures (15 – – – – – or · · · · ·) actually represents homaline is not yet decided.

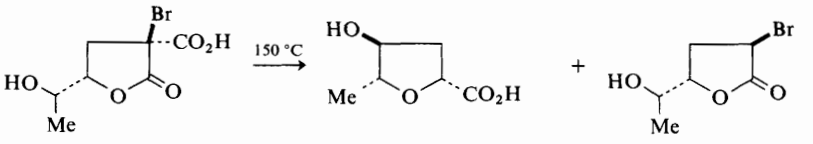
19

Miscellaneous Alkaloids

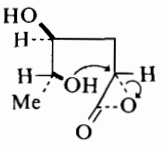
BY V. A. SNIECKUS

1 Muscarine Alkaloids

A review concerning the chemistry, biogenesis, and pharmacology of *Amanita muscaria* components includes a comprehensive coverage of the muscarine alkaloids.[1] (+)-*R*-4-Hydroxypyrrolidin-2-one has been isolated from this source.[2] A method for the identification of stereoisomeric muscarines by combination vacuum pyrolysis–g.c. analysis has been described.[3] A micro method for the determination of ibotenic acid and other 3-hydroxyisoxazoles has been developed.[4] Stereospecific syntheses for DL-muscarine and DL-*allo*-muscarine have been reported.[5] Pyrolysis of (1) yielded the carboxylic acid (2) and the bromolactone (3) which served as key compounds in the synthesis of the muscarines. The minor component (3) was shown to be an intermediate in the formation of (2) and therefore the conversion [(3)→(2)] could be written as an intramolecular S_N2 displacement on an α-lactone (4). However, treatment of (3) with



(1) (2) (3)



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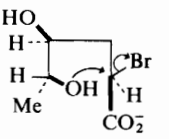


(5)

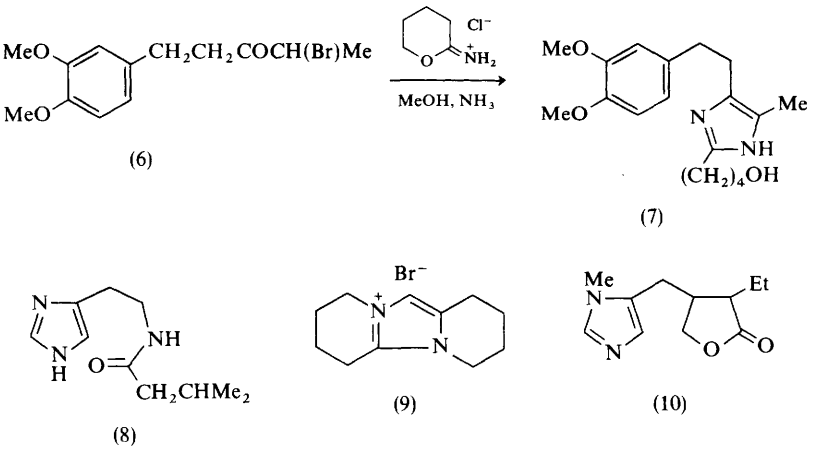
[1] C. H. Eugster, *Fortschr. Chem. Org. Naturstoffe*, 1969, **27**, 261.
[2] T. Matsumoto, W. Trueb, R. Gwinner, and C. H. Eugster, *Helv. Chim. Acta*, 1969, **52**, 716.
[3] C. H. Eugster and E. Schleusener, *Helv. Chim. Acta*, 1969, **52**, 708.
[4] M. Frater-Schroder, R. Good, and C. H. Eugster, *Helv. Chim. Acta*, 1969, **52**, 720.
[5] T. Matsumoto, A. Ichihara, and N. Ito, *Tetrahedron*, 1969, **25**, 5889.

base yielded a mixture of acids (2) epimeric at the carbon atom adjacent to the carbonyl function. Thus, the mechanism of this reaction could be written as proceeding through (5).

2 Imidazole Alkaloids

Several novel members have been added to this relatively small group of alkaloids.[6] One of these is cypholophine (7) which was synthesised in low overall yield [(6) → (7)].[7] Dolichotheline (8) has been isolated from a cactus plant and its structure has been confirmed by synthesis.[8] The *Lolium* species has yielded histamine among a fascinating variety of other types of alkaloids;[9] N^{α}-cinnamoylhistamine has been isolated from *Sterculiaceae* plants.[10] The structure of the unusual imidazole alkaloid (9) has been confirmed by *X*-ray analysis.[11] A synthesis of a properly functionalised lactone for incorporation into pilocarpine (10) has been reported,[12] and the decomposition of the latter in aqueous solution has been studied.[13]

The sensitised photolysis of *N*-benzoylhistidine yielded a total of sixteen products some of which are dimers.[14]



[6] M. Luckner in 'Biosynthese der Alkaloide,' ed. K. Mothes and H. R. Schütte, Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 593.
[7] N. K. Hart, S. R. Johns, J. A. Lamberton, J. W. Loder, and R. H. Nearn, *Chem. Comm.*, 1970, 441.
[8] H. Rosenberg and A. G. Paul, *Tetrahedron Letters*, 1969, 1039; H. Rosenberg and A. G. Paul, *Phytochemistry*, 1970, **9**, 655.
[9] J. A. D. Jeffreys, *J. Chem. Soc.* (*C*), 1970, 1091.
[10] S. R. Johns, J. A. Lamberton, J. W. Loder, A. H. Redcliffe, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 1309.
[11] E. Soderberg and P. Kierkegaard, *Acta Chem. Scand.*, 1970, **24**, 397.
[12] A. V. Chumachenko, E. N. Zvonkova, and N. A. Preobrazhenskii, *Zhur. org. Khim.*, 1969, **5**, 582.
[13] K. Baeschlin, J. C. Etter, and H. Moll, *Pharm. Acta Helv.*, 1969, **44**, 301.
[14] M. Tomita, M. Irie, and T. Ukita, *Tetrahedron Letters*, 1968, 4933.

3 Purine Alkaloids

Leading chemical references may be obtained from a recent review.[15] A review of the analytical methods of purine alkaloid determination is not readily accessible.[16] Caffeine has been isolated from *Banisteriopsis inebrians*, a species which also produces simple indole alkaloids.[17]

Among the new reports[18–20] of synthetic interest, the preparation of D- and L-*threo*-lentysine offers instructive carbohydrate chemistry.[20]

Prototropic equilibria of purine alkaloids have been studied.[21]

4 Colchicine Alkaloids

Reviews of this group are available;[22,23] in one of these, coverage is limited to alkaloids elaborated by the Wurmbaeoideae plants.[23] Several new reports concerning exhaustive isolation studies of *Colchicum* species[24,25] as well as of *Kreysigia multiflora*,[24] *Merendera filifolia*,[24] and *M. jolantae*[26] plants have appeared. For the most part, known colchicine alkaloids have been found although structures of several new ones have not been defined. A study of composition of alkaloids in *Colchicum luteum* at various stages of development has been described.[27]

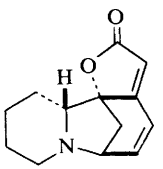
Evidence for the stereoisomeric relationship between β- and γ-lumicolchine, photolysis products of colchicine, has been obtained.[28]

5 Securinine Alkaloids

This relatively large and interesting group has not been reviewed.[29] Fifty *Securinega* species have been screened for securinine (11) content.[30] The optical

[15] M. Luckner, in 'Biosynthese der Alkaloide,' ed. K. Mothes and H. R. Schütte, Deutscher Verlag der Wissenschaften, Berlin, 1969, p. 568.
[16] M. Struhar, *Acta Fac. Pharm. Univ. Comeniana*, 1968, **16**, 147.
[17] F. D. O'Connell, *Naturwiss.*, 1969, **56**, 139.
[18] J. Klosa, *J. prakt. Chem.*, 1969, **311**, 193.
[19] K. H. Kleine, G. Graefe, and R. Haller, *Arch. Pharm.*, 1969, **302**, 16.
[20] M. Hashimoto, Y. Saito, H. Seki, and T. Kamiya, *Tetrahedron Letters*, 1970, 1359.
[21] H. Stamm, *Annalen*, 1970, **731**, 174; A. Albert, *Chem. and Ind.*, 1970, 365.
[22] W. C. Wildman and B. A. Pursey, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1968, vol. XI, p. 407; T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969, p. 222.
[23] P. Manitto, *Fitoterapia*, 1968, **39**, 4 (*Chem. Abs.*, 1969, **71**, 46654k).
[24] H. Potesilova, C. Alcaraz, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1969, **34**, 2128.
[25] H. Potesilova, J. Santavy, A. El-Hamidi, and F. Santavy, *Coll. Czech. Chem. Comm.*, 1969, **34**, 3540; H. Potesilova, J. Wiedermannova, and F. Santavy, *ibid.*, 1969, **34**, 3642.
[26] B. Chommadov, M. K. Yusupov, and A. S. Sadykov, *Khim. prirod. Soedinenii*, 1969, **5**, 457.
[27] A. S. Sadykov, M. K. Yusupov, and B. Chommadov, *Rast. Resur.*, 1969, **5**, 441 (*Chem. Abs.*, 1970, **72**, 39785w).
[28] L. Canonica, B. Danieli, P. Manitto, and G. Russo, *Tetrahedron Letters*, 1969, 607.
[29] Z. Horii, M. Ito, and M. Hanaoka, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 1754.
[30] Z. Kowalewski, I. Frencel, I. Urszulak, and A. Filarowska, *Ann. Pharm. (Poznan)*, 1969, **7**, 99.

antipode (12) of a known alkaloid, norsecurinine, has been isolated.[31] A securinine subunit (13) has been synthesised *via* an intramolecular Michael reaction.[32]



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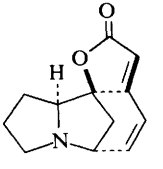


(12)

(13)

6 Unclassified Alkaloids

New alkaloids which are unclassified are listed according to plant species herein. If an alkaloid or its relative has been previously discussed in Manske,[33] this reference is given in parentheses following the botanical name.

Aeglopsis chevalieri Swing. (Rutaceae) (ref. 33*b*, p. 565)

A new derivative of halfordinol (14, R = H), originally discovered in *Halfordia scleroxyla* F. Muell,[33b] has been shown to be a mixture of isomeric olefins [14, R = $-CH_2{\cdot}CH{=}CMe_2$ and $-CH_2CH_2{\cdot}C(Me){=}CH_2$] by n.m.r. spectroscopy.[34]

Alchornea javensis (Bl.) Muell.-Arg. (Euphorbiaceae)

Two new hexahydroimidazopyrimidines [15, $R^1 = -C(Me){=}CH_2$, $R^2 = R^3 = H$ and $R^1 = H$, $R^2 = -C(Me){=}CH_2$, $R^3 = -COCH{=}CMe_2$] have been characterised by spectral and chemical methods.[35] Additionally, 2,2-dimethylacrylamide and two guanidine alkaloids (see *Pterogyne nitens*) have been shown to be constituents of this species.

Aspergillus phoenicis (Aspergillaceae)

Nigragilline has been shown to possess structure (16) by spectral and degradative means and by total synthesis.[36]

Codonopsis clematidea

The structure previously assigned[37a] to codonopsine has been revised[37b] to (17) on the basis of its n.m.r. spectrum and a Hofmann degradation.

[31] R. Rouffiac and J. Parello, *Plant. Med. Phytother.*, 1969, **3**, 220.
[32] R. Furstoss, P. Teissier, and B. Waegell, *Chem. Comm.*, 1970, 384.
[33] [a] R. H. F. Manske, 'The Alkaloids,' Academic Press, New York, 1970, vol. XII; [b] *ibid.*, vol. X.
[34] D. L. Dreyer, *J. Org. Chem.*, 1968, **33**, 3658.
[35] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Chem. Comm.*, 1969, 1484.
[36] F. Caesar, K. Jansson, and E. Mutschler, *Pharm. Acta Helv.*, 1969, **44**, 676.
[37] [a] S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 30; [b] S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, *ibid.*, p. 606.

Dendrobium pierardii Roxb. (Orchidaceae)

The phthalide alkaloid (18) has been isolated.[38]

Halfordia scleroxyla F. Muell. and *H. kendack* (Rutaceae) (ref. 33*b*, p. 565)

Details concerning the structural elucidation of the pyridine-oxazole alkaloids (14) have been reported.[39] Interestingly, furoquinolines are found in the same plant species.

Leonurus sibiricus L. (ref. 33*b*, p. 570.)

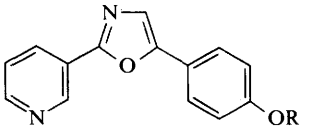
The structure of leonurine has been revised (19) and three methods for its synthesis have been described.[40]

Liparis spp. (Orchidaceae) (ref. 33*a*, p. 315)

Details concerning the structural elucidation[41a] of kuramerine (20, R = glucose), and the synthesis [41b] of tetra-acetylkuramerine have been reported.

Lolium perenne L. (Gramineae) (ref. 33*b*, p. 574)

Aside from histamine, pyrrolizidine, quinoline and indole alkaloids, annuloline (21) has been isolated.[42]



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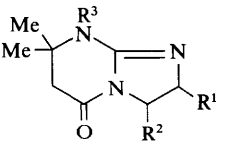

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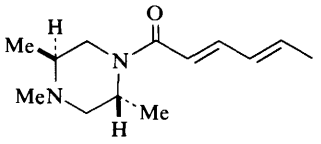

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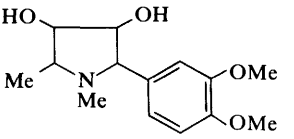

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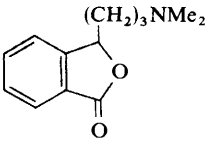

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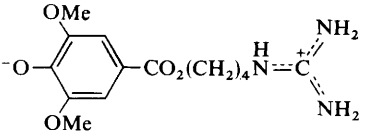
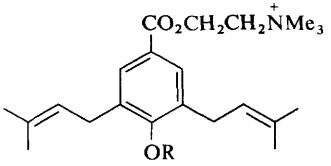


(19)

[38] M. Elander, K. Leander, and B. Lüning, *Acta Chem. Scand.*, 1969, **23**, 2177.
[39] W. D. Crow and J. H. Hodgkin, *Austral. J. Chem.*, 1968, **21**, 3075.
[40] S. Sugiura, S. Inoue, Y. Hayashi, Y. Kishi, and T. Goto, *Tetrahedron*, 1969, **25**, 5155.
[41] [a] K. Nishikawa, M. Miyamura, and Y. Hirata, *Tetrahedron*, 1969, **25**, 2723; [b] H. Tanino, S. Inoue, K. Nishikawa, and Y. Hirata, *ibid.*, 1969, **25**, 3033.
[42] J. A. D. Jeffreys, *J. Chem. Soc.* (*C*), 1970, 1091.



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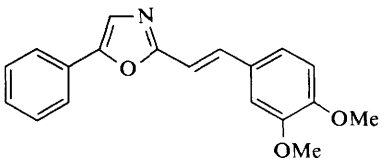


(21)

Lunaria biennis Moench. (*L. annua L.*) (Cruciferae) (ref. 33*b*, p. 572)

Two new compounds have been obtained which exhibit a CH_2 bridge from N to ring C (22), a structural complication not encountered in previously-isolated alkaloids from this species.[43]

Macrorungia longistrobus C.B.Cl. (Acanthaceae)

Three interesting tetrahydroquinolylimidazole alkaloids, *e.g.*, longistrobine (23), have been characterised.[44] Dehydrolongistrobine (24), a derivative of (23), undergoes a retro-Michael reaction upon treatment with acid to yield, in addition to succinic acid, macrorine (25), which is itself a *bona fide* alkaloid.

Pentaclethra macrophylla Benth. (Leguminosae)

Paucine has been assigned structure (26) mainly on the basis of its mass spectrum.[45]

Pisum sativum L. (Leguminosae)

Pyrazine derivatives [27, R = $CHMe_2$, CH(Me)Et, and CH_2CHMe_2] may be responsible for the flavour of this species (green peas).[46]

Pterogyne nitens Tul. (Leguminosae)

Two alkaloids which form explosive salts have been identified as the guanidine derivatives pterogynine (28) and pterogynidine (29).[47,48] The latter compound is believed to be identical to a guanidine alkaloid isolated from *Alchornea javensis*.[35] The structure of pterogynine (28) was confirmed by synthesis.[48]

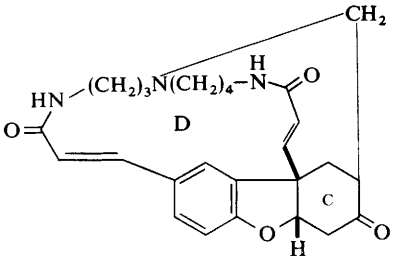
Sibara virginica (L.) Rollins (Cruciferae)

A new type of plant constituent, isoferulic acid choline ester (30), has been isolated.[49]

Withania somnifera Dun. (Solanaceae) (ref. 33*b*, p. 587)

The unique pyrazole alkaloid, withasomnine (33), has been independently synthesised by two groups in not less than four routes.[50,51] One of these[50] uses

[43] C. Poupat, B. Rodriguez, H.-P. Husson, P. Potier, and M.-M. Janot, *Compt. rend.*, 1969, **269**, *C*, 335.
[44] R. R. Arndt, S. H. Eggers, and A. Jordaan, *Tetrahedron*, 1969, **25**, 2767.
[45] A. Hollerbach and G. Spiteller, *Monatsh.*, 1970, **101**, 141.
[46] K. E. Murray, J. Shipton, and F. B. Whitfield, *Chem. and Ind.*, 1970, 897.
[47] R. A. Corral, O. O. Orazi, and M. F. de Petruccelli, *Experientia*, 1969, **25**, 1020.
[48] R. A. Corral, O. O. Orazi, and M. F. de Petruccelli, *Chem. Comm.*, 1970, 556.
[49] R. Gmelin and A. Kjaer, *Phytochemistry*, 1970, **9**, 667.
[50] A. Morimoto, K. Noda, T. Watanabe, and H. Takasugi, *Tetrahedron Letters*, 1968, 5707.
[51] T. Onaka, *Tetrahedron Letters*, 1968, 5711.



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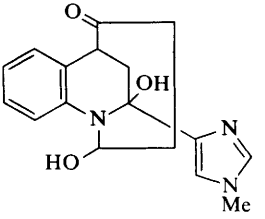

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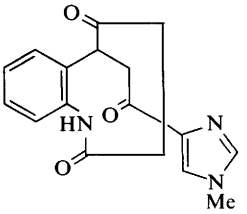

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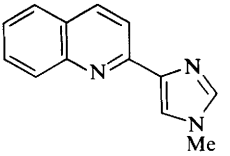

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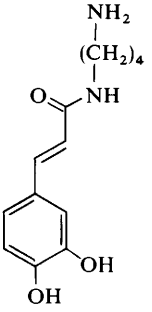

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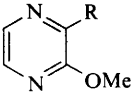

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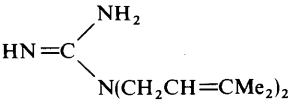

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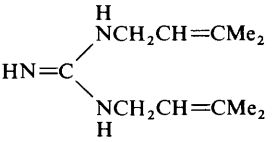
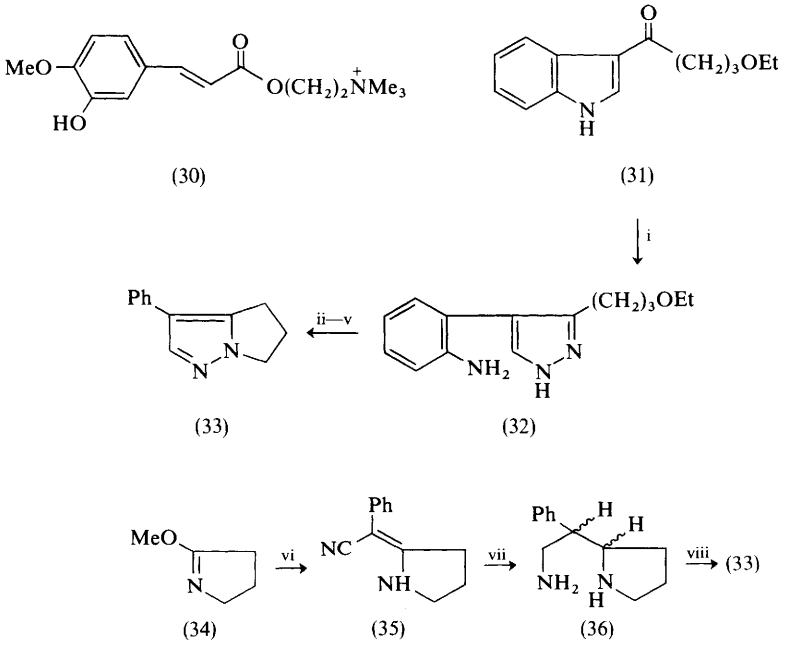


(29)

the indole derivative (31) as an intermediate which is converted into the pyrazole (32). Standard removal of an aromatic amino-function followed by cyclisation yields (33). Another route[51] follows proposed biogenetic lines. Two steps



Reagents: i, NH_2NH_2, H_2O; ii, HNO_2; iii, H_3PO_2; iv, 47% HBr; v, KOH; vi, $PhCH_2CN$, NaH, THF; vii, PtO_2, H_2, HCl, EtOH; viii, NaOCl, H_2O, MeOH.

[(34) → (35) → (36)] lead to a crude diamine which is oxidatively cyclised to (33) in 7.5% yield.

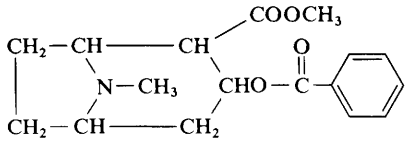
20

Pharmacologically Interesting and Clinically Useful Alkaloids

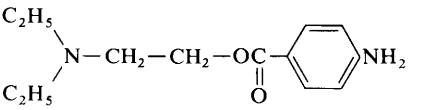
BY E. SCHLITTLER

The discovery of morphine by Sertürner (1809—1817) stimulated an enormous activity in the field of plant products and most alkaloids still used today were found during the first half of the last century. The years to follow were not so productive, ephedrine being isolated in 1887 and scopolamine in 1888, and of all the alkaloids found in the first half of the 20th century, only the ergot alkaloids and (to some limited extent) lobeline from *Lobelia inflata* (Campan.) have found use in human therapy.

In spite of this definite downward trend in new discoveries, the chemistry of therapeutically useful compounds has gained enormously from the achievements of basic alkaloidal research. By molecular modification of genuine alkaloids other therapeutically useful compounds could be prepared (*e.g.* morphine → codeine, cephaeline → emetine, colchicine → demecolcine, thebaine → oxycodone) and, even more important, a great number of synthetics, tailored after natural alkaloids, have been prepared, pharmacologically tested, and in some cases found to be active. The most impressive example of the similarity of action is certainly the one between cocaine (1) (genuine alkaloid) and procaine (2) (model compound), but it is morphine which has stimulated the greatest amount of synthetic research in order to obtain active analgesic compounds, possibly free of the serious side-reactions of the genuine opium alkaloid.



(1)



(2)

The discovery of reserpine in 1952 has had a deep influence on the attitude of chemists and biologists. This is a genuine alkaloid with wide therapeutic possibilities whose world sales reached the 100 million dollar line within a few years of discovery. In view of the small percentage of plants investigated until then, and the many plants possessing some folkloristic merits, it was argued the field might still become prolific, if only this kind of research were intensified. Most of the bigger pharmaceutical companies at that time became active in the search for new plant products and great sums of money were invested for this purpose. Botanical expeditions were sent to tropical regions to procure and investigate as many interesting plants as possible; a considerable number of botanical surveys were published as a consequence of these developments. Alkaloid chemistry in general gained greatly from this search, but many money-minded pharmaceutical companies became disappointed since the financial reward was extremely small.

Since then, more active synthetic tranquillisers have replaced reserpine, but it does still have some uses. The sales of reserpine in its finished form are probably higher than those of any other genuine alkaloid. The purpose of this review, which is strictly 'post-reserpine', is to demonstrate that interesting work is being done in this field, although no major new alkaloid has been discovered during the last 8—10 years.

Screening results in animals or humans must be interpreted with great care because of the uncertainties due to the reaction variations, both inter- and intra-species. Often it happens that the importance of some screening result is over-emphasised and only corrected in later years, whereas another result is not appreciated at an early moment. Certainly this report may suffer from such shortcomings.

1 Hallucinogens

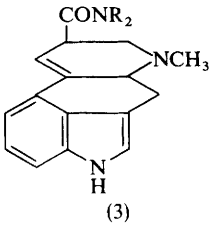
A statement has been made that 'there is an acute need for the active principles present in hallucinogenic plants, both as potentially useful drugs in the treatment of mental disease and as a new tool for the pharmacologist in his attempts to shed new light on the biochemical causes of mental illness'.[1] Nitrogenous hallucinogens have been investigated very actively during recent years, although the goals put forward in the above quotation have not fully been reached.

Two reviews on hallucinogenic plant materials have appeared recently,[1,2] in addition to a book entirely devoted to this problem.[3]

There are three classes of compounds which have been studied most extensively, *viz.* hallucinogens from lysergic acid, simpler indoles, and derivatives of mescaline and amphetamine.

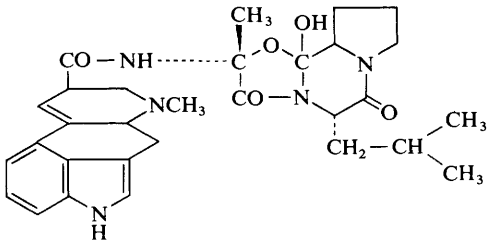
[1] N. R. Farnsworth, *Science*, 1968, **162**, 1086.
[2] R. E. Schultes, *Science*, 1969, **163**, 245.
[3] 'Ethnopharmacologic Search for Psychoactive Plants,' ed. D. E. Efron, B. Holmstedt, and N. S. Kline, U.S.P.H. Service Publication No. 1645, Gov. Print. Off., Washington D.C., 1967.

Lysergic acid diethylamide, LSD (3a), the best known hallucinogenic derivative of lysergic acid, was synthesised by Hofmann[4] in 1943. However, its impact has been such that pharmacological and clinical studies are still carried on most actively and the properties of this compound have stimulated research in this field tremendously. Of great importance was Hofmann's discovery that lysergic acid is not exclusively a product of Agararicaceae (mushrooms), but that this tetracyclic indole ring system can also be synthesised by higher plants. This was proved by the isolation of lysergic and isolysergic acid amide (3b) (ergine and erginine), together with chanoclavine (4), from *Ipomoea* and *Rivea*, two Convolvulaceae.[5] Additional clavine alkaloids were later obtained from the same two genera, and these results have been confirmed and extended by many other researchers.[6]

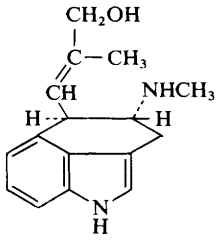


(3)

(a) R = C_2H_5; LSD
(b) R = H; Lysergic acid amide



(5)



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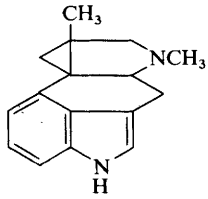


(6)

[4] A. Stoll and A. Hofmann, *Helv. Chim. Acta*, 1943, **26**, 944.

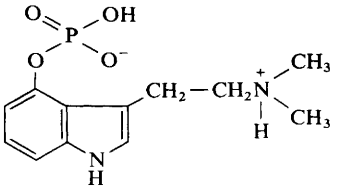
[5] A. Hofmann and H. Tscherter, *Experientia*, 1960, **16**, 414; A. Hofmann, *Planta Medica*, 1961, **9**, 354.

[6] *e.g.*, W. A. Taber, L. C. Vining, and R. A. Heacock, *Phytochemistry*, 1963, **2**, 65; D. Groeger, *Flora (Jena)*, 1963, **153**, 373 (*Chem. Abs.*, 1964, **60**, 2043); H. C. Beyerman and A. van de Linde, *Chem. Weekblad*, 1963, **59**, 508; J. W. Hylin and D. P. Watson, *Science*, 1965, **148**, 499; A. D. Marderosian and H. W. Youngken, *Lloydia*, 1966, **29**, 35; K. Genest and M. R. Sahasrabhude, *Econ. Bot.*, 1966, **20**, 416; A. D. Marderosian, *Amer. J. Pharm.*, 1967, **139**, 19; T. Niwaguchi and T. Inoue, *J. Chromatog.*, 1969, **43**, 510.

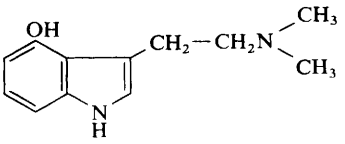
In addition, the Hofmann group isolated ergosine (5) and ergosinine from *Ipomoea argyrophylla* and *I. hildebrandtii*,[7] and later cycloclavine (6).[8] Thus it has been shown that certain Convolvulaceae are not only able to build up lysergic acid, but also ergot alkaloids of higher molecular weight with a complicated polypeptide nucleus.

This was the unexpected solution of a problem which had puzzled researchers for centuries. In 1651 Hernandez, in his book on Mexican medical preparations,[9] gave a drawing of the plant whose seeds were called 'Ololuiqui' and he described how Mexican priests swallowed Ololuiqui seeds if they wanted to get in touch with their gods.[10] For more than 400 years the identity of the plant with the hallucinogenic seeds was doubtful until R. E. Schultes and H. Osmond[11] showed that the two plants were *Ipomoea* and *Rivea*, and thus the road for systematic chemical studies was opened.

Even more interesting was the problem of 'Teonanacatl, the god-like mushroom' of the old Mexicans. For an excellent review on the story of the Mexican mushrooms see Hofmann.[12] Here again, it was only in 1939 that some of the mushrooms were identified.[13] Much of the basic work was done by R. G. Wasson and Mrs. Wasson and by R. Heim, and today at least 24 species, belonging to 5 genera, are known to produce hallucinogenic indoles, *Psilocybe* and *Panaeolus* being the most important ones. It was the Hofmann group of Sandoz again that isolated the two active principles, psilocybine (7) and psilocine (8), simple 4-hydroxy-*NN*-dimethyltryptamines.[14] The following structures were assigned to these two compounds:



(7)



(8)

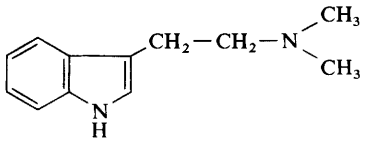
The dried mushrooms contain about 0.2—0.4 % psilocybine, the psilocine content being minimal. The activity of psilocybine is much lower than that of LSD, the

[7] D. Stauffacher, H. Tscherter, and A. Hofmann, *Helv. Chim. Acta*, 1965, **48**, 1379.
[8] D. Stauffacher, P. Niklaus, H. Tscherter, H. P. Weber, and A. Hofmann, *Tetrahedron*, 1969, **25**, 5879.
[9] F. Hernandez, 'Rerum medicarum Novae Hispaniae thesaurus,' 1651.
[10] *cf.* R. E. Schultes, *Planta Medica*, 1965, **13**, 125.
[11] H. Osmond, *J. Ment. Sci.*, 1955, **101**, 526.
[12] A. Hofmann, *Chimia (Switz.)*, 1960, **14**, 309.
[13] R. E. Schultes, *Bot. Mus. Leafl. Harvard Univ.*, 1939, **7**, 37; *Amer. Anthrop.*, 1940, **42**, 429.
[14] A. Hofmann, R. Heim, A. Brack, and H. Kobel, *Experientia*, 1958, **14**, 107; A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, T. Petrzilka, and F. Troxler, *Helv. Chim. Acta*, 1959, **42**, 1557.

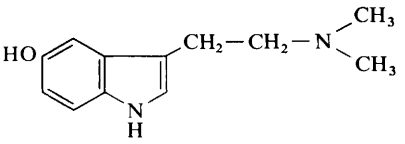
active oral dose being 60—200 $\mu g\ kg^{-1}$ or 5—10 mg sublingually.[15] Neither of these two compounds is used for any practical purpose.

Psilocybine can be obtained by total synthesis or from submerged culture of *Psilocybe cubensis*;[16] psilocine has recently been obtained, albeit in low yields, by direct oxidation of *NN*-dimethyltryptamine by the Fenton–Cier reagent.[17]

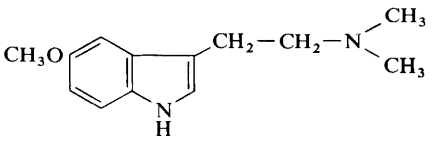
Even simpler indoles with hallucinogenic properties have been isolated from Leguminosae and Myristicaceae, plant material which is sniffed or inhaled by South American Indians to produce visions and hallucinations. Several Leguminosae, including *Piptadenia* species, have been used, whereas the only Myristicaceae used for its hallucinogenic activity is *Virola theiodora.* Three highly interesting reviews on the use of South American snuffs, on their botanical origins, and their chemical constituents and pharmacology have been written by Wassén, by Schultes and Holmstedt, and by Lindgren.[3] The indoles isolated from *Piptadenia* were *NN*-dimethyl- (9) or *N*-methyl-tryptamines, unsubstituted in ring A or having 5-methoxy- (10) or 5-hydroxy-substituents (11) (bufotenine):



(9)

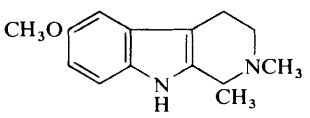


(11)



(10)

Identical compounds have been isolated from *Virola theiodora*, the *NN*-dimethyltryptamine content usually being highest.[18] From the same plant also, 1,2-dimethyl-6-methoxytetrahydro-β-carboline (12) has been isolated,[19] whose



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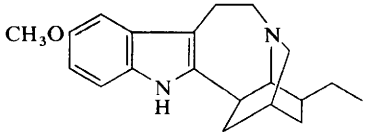
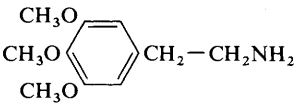


(13)

[15] L. E. Hollister, *Arch. Internat. Pharmacodyn.*, 1961, **130**, 42.
[16] P. Catalfomo and V. E. Tyler, *Lloydia*, 1964, **27**, 53.
[17] M. Julia and F. Ricalens, *Compt. rend.*, 1969, **269***C*, 51.
[18] S. Agurell, B. Holmstedt, J. E. Lindgren, and R. E. Schultes, *Acta Chem. Scand.*, 1969, **23**, 903.
[19] S. Agurell, B. Holmstedt, J. E. Lindgren, and R. E. Schultes, *Biochem. Pharmacol.*, 1968, **17**, 2487.

structure possesses elements of the structure of ibogaine (13); this latter is an indole alkaloid obtained from *Tabernanthe iboga*, a plant used as a stimulant by the natives of Western Africa.

Another plant whose parts have been used for centuries to cause hallucinations is the cactus *Lophophora Williamsii* (Peyotl or Peyote). Its contents have long been known, mescaline (14) being the active ingredient.



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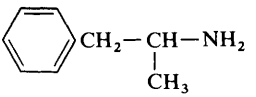
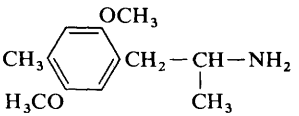


(15)

Closely related to mescaline is amphetamine (15), probably the best known synthetic stimulant. Both types of compounds, the β-phenylethylamine (mescaline) and the phenylisopropylamine (amphetamine) have been studied very broadly, one type of compound stimulating interest in the other one. It has been shown that the activities of the two types, having identical substitution at the benzene ring, can vary considerably.

One of the most interesting compounds, an amphetamine derivative with a mescaline-like substitution of the benzene ring, is STP or DOM (16), much in demand by the present-day 'hippie generation'.[20] The hallucinogenic activity



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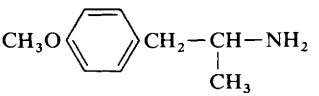


(17)

of DOM is so strong and lasts so long, and therefore has such an abuse potential, that in the U.S.A. it may not be used for any clinical testing in man or in animals or for tests *in vitro* without prior approval by the Commissioner of the Food and Drug Administration.[21]

Similar work has been carried out with simple β-phenylethylamines of the mescaline type,[22] whose activities seemed to be more restricted than the amphetamine derivatives. Only 2,3,4,5-tetramethoxy- and 2,3,4,5,6-pentamethoxy-

[20] S. H. Snyder, L. Faillace and L. E. Hollister, *Science*, 1967, **158**, 669; G. F. Phillips and R. J. Mesley, *J. Pharm. Pharmacol.*, 1968, **21**, 9; J. E. Idanpaan, W. M. McIsaac, B. T. Ho, G. E. Fritchie, and L. W. Tansey, *Science*, 1969, **164**, 1085.

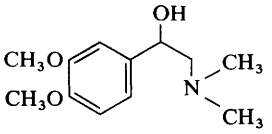
[21] Fed. Reg. 1968, 6/13 (*Chem. Abs.*, 1968, **69**, 34 458*v*).

[22] J. R. Smythies, R. J. Bradley, V. S. Johnston, F. Benington, R. D. Morin, and L. C. Clark, *Psychopharmacologia*, 1967, **10**, 379.

phenylethylamines produce an effect similar to mescaline, whereas all other compounds with fewer substituents, or those in which the 3,4,5-positions are not occupied, are inactive. In the amphetamine series, a single 4-methoxy-group (17) suffices to make the compound strongly hallucinogenic.[23]

Hallucinogenic properties have been claimed[24] for two newly-isolated cactus alkaloids of somewhat unusual constitution, macromerine (18) and gigantine (19).

Certainly some of these hallucinogenic products have become interesting research tools in the hands of pharmacologists and psychiatrists, but any claim that they have become potentially useful drugs in the treatment of mental disease is premature.



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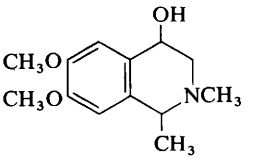


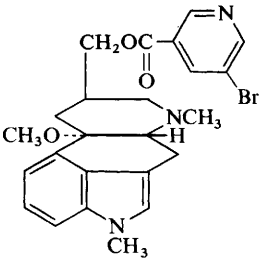
(19)

2 Ergot Alkaloids

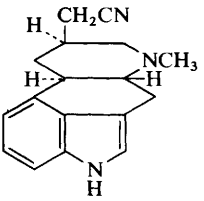
During the last twenty years the saprophytic culture of ergot alkaloids has been studied by numerous investigators. The most important progress was made in 1960 when an Italian group[25] succeeded in growing *Claviceps paspali* in a submerged culture, and thus was able to obtain lysergic and isolysergic acid amides and other lysergic acid derivatives in yields of 1 mg ml^{-1} and above.[26] Thus lysergic acid became relatively easily available as a starting material for additional semi-synthetic derivatives. L. Bernardi[27] has reviewed recent work in this field; from the same group also originated a new vasodilating and α-receptor blocking ergoline derivative MNE (20), 1,6-dimethyl-8β-(5-bromonicotinoyloxymethyl)-10α-methoxyergoline,[28] which is currently under clinical study as a vasoactive substance.

No new clinically interesting products have resulted from the Sandoz (Stoll–Hofmann) group recently, but a Czech group has studied the two new ergoline ureas Lysenyl (21) and Mesenyl (22): the former has been introduced as an anti-migraine preparation.[29] For some ergot alkaloids, especially ergocornine, ergo-

[23] J. R. Smythies, V. S. Johnston, and R. J. Bradley, *Nature*, 1967, **216**, 128.
[24] J. E. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Letters*, 1967, 1321; L. Grethe, M. Uskokovic, T. Williams, and A. Brossi, *Helv. Chim. Acta*, 1969, **50**, 2397.
[25] F. Arcamone, C. Bonino, E. B. Chain, A. Ferretti, P. Pennella, A. Tonolo, and L. Vero, *Nature*, 1960, **187**, 238; for a more detailed study see *Proc. Roy. Soc.*, 1961, **B155**, 26.
[26] E. B. Chain, A. Tonolo, and C. Bonino, Ger. P. 1 140 670, Dec. 6, 1962.
[27] L. Bernardi, *Chimica e Industria*, 1969, **51**, 563.
[28] G. Arcari, L. Dorigotti, G. B. Fregnan, and A. H. Glaesser, *Brit. J. Pharmacol.*, 1968, **34**, 700 P.
[29] I. Podvalova and M. Vojtechovsky, *Arzneimittel-Forsch.*, 1966, **16**, 220; M. Semonsky, V. Zikan, Z. Votava, I. Podvalova, and K. Ponek, *Czech. Farm.*, 1968, **17**, 296 (*Chem. Abs.*, 1969, **70**, 1976); *Pharmazie*, 1968, **23**, 147.



(20)



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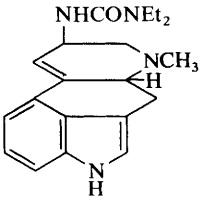
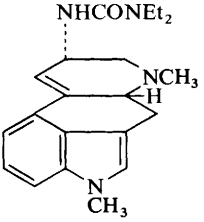


(21)



(22)

crystine, 2-bromo-α-ergocryptine, and D-6-methyl-8-cyanomethylergoline (23), antifertility effects have been claimed. This was first observed in 1955,[30] but the problem is still under discussion.[31]

Lysergic acid amide (LSD) might be responsible for chromosomal damages, but the significance of this finding is unknown at present.[32]

3 Analgetics and Anti-inflammatory Compounds

Analgetics.—The analgetic activity of morphine greatly stimulated molecular modification of its structure, even before all its details were known. Thus, a great number of clinically used morphine derivatives with only marginal advantages over morphine have been prepared during the last 70 years.[33] Besides their

[30] M. C. Shelesnyak, *Amer. J. Physiol.*, 1955, **180**, 47.

[31] R. Iizucka and H. Koi, *Jap. J. Fertility and Sterility*, 1968, **13**, 326 (*Chem. Abs.*, 1969, **70**, 56 172*v*); E. Flueckiger and H. R. Wagner, *Experientia*, 1968, **24**, 1130; K. Rezabek, M. Semonsky, and N. Kucharczyk, *Nature*, 1969, **221**, 666; G. Carpent and L. Desclin, *Endocrinology*, 1969, **84**, 315.

[32] R. S. Sparkes, J. Melnyk, and L. P. Bozetti, *Science*, 1968, **160**, 1343; W. Kruskal and S. Haberman, *ibid.*, 1968, **162**, 1508, 1509; R. Auerbach and J. A. Rugowski, *ibid.*, 1967, **157**, 1325.

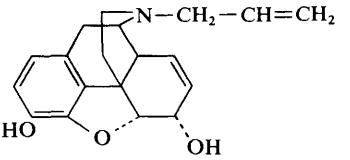
[33] See *e.g.*, E. L. May, in 'Medicinal Chemistry,' ed. A. Burger, 3rd edn., Interscience, New York–London, 1970, p. 1327 ff.; E. L. May and L. J. Sargent, in 'Analgesics,' ed. G. deStevens, Academic Press, New York–London, 1965, p. 123 ff.

enhanced or at least modified activity, these compounds possessed the same side-reactions as morphine, *viz.* spastic constipation, depression of the respiratory centre, sedation, euphoria, and addiction.

Other series of synthetic analgetics, intentionally or unintentionally patterned after the morphine structure, were the meperidines (including ketobemidone), the methadones (including propoxyphene), and the morphinans. These newer compounds have more or less the same disadvantages as morphine, which limits their use. Within this much investigated series of compounds, a clear-cut dissociation of the different effects of morphine proved to be impossible.

The Narcotic Antagonists.[34] A narcotic antagonist is a compound which can reverse the more prominent effects of morphine-like analgesia, respiratory depression, and causes withdrawal symptoms when given to narcotic addicts. Primarily, such compounds are found by reversal of analgesia as measured by the tail-flick method in rats or mice. It is evident that a positive or negative tail-flick test does not account for any other pharmacologic activities, and that a detailed pharmacologic analysis is necessary.

In 1915, Pohl[35] reported the morphine antagonistic properties of *N*-allylnorcodeine. This and additional observations remained unnoticed until the early 1940s, when the synthesis and the pharmacological properties of *N*-allylmorphine (24) (nalorphine) became known.[36] The highly specific ability of nalorphine to reverse the depressant effects of morphine made it the drug most used in the treatment of narcotic overdosage. Nalorphine was found to be non-addicting and, strangely enough, still analgetically active in man. However, some psycho-



(24)

mimetic effects inherent to nalorphine and some of its congeners prevented their use as analgetics. Clearly enough, some dissociation of the activities of the genuine morphine derivatives mentioned had taken place: in humans (contrary to animals) the analgetic effect was still present, addiction had disappeared, respiration depression seemed to be lessened, but psychomimetic effects, less known with morphine, had appeared.[37]

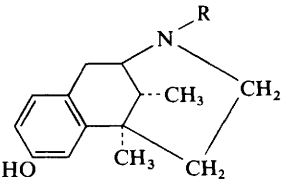
[34] See S. Archer and L. S. Harris, 'Narcotic Antagonists' in *Progress of Drug Research*, ed. E. Jucker, Birkhäuser Verlag, Basel–Stuttgart, 1965, **8**, 261.

[35] J. Pohl, *Z. Exp. Path. Therap.*, 1915, **17**, 370 (*Chem. Abs.*, 1917, 1488).

[36] A. A. Pessolano, J. Weijlard, and K. Pfister, *J. Amer. Chem. Soc.*, 1953, **75**, 4963; J. Weijlard, P. D. Orahovats, A. P. Sullivan, G. Purdue, F. K. Heath, and K. Pfister, *ibid.*, 1956, **78**, 2342.

[37] See Table 6, p. 286 of ref. 2.

These interesting results have given a renewed stimulus to research in this field. The problem of narcotic antagonists has been studied most extensively with genuine morphine alkaloids and the benzomorphans. The development of the benzomorphans really dates back to the 1950s and is beyond the limits of our discussions, whereas the development of the two most important representatives, pentazocine (25) and cyclazocine (26), into clinically usable products is still a matter of discussion.



(25) R = $-CH_2-CH=CMe_2$
(26) R = $-CH_2-CH(CH_2)_2$

In humans cyclazocine is said to be *ca.* 40 times more potent analgetically than morphine when given subcutaneously or orally.[38] At equi-analgetic doses it produces the same degree of respiratory depression as morphine does. Tolerance also develops[39] and at high doses mild withdrawal symptoms appear. It also produces a high enough number of psychomimetic effects to make cyclazocine unacceptable as a general analgetic, but its use for special cases is advocated.[40] Pentazocine is less active than cyclazocine, but seems to be remarkably free of psychomimetic properties. Like morphine, pentazocine produces some degree of respiratory depression. Intravenously, it is *ca.* 3—4 times less active than morphine.

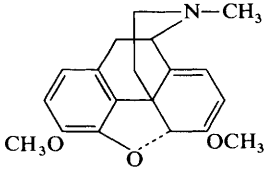
In later investigations (1966) the impression that cyclazocine was not suitable as an analgetic was confirmed, but its use for the treatment of narcotic addicts was still favoured.[41] The possibilities for pentazocine looked much brighter, and in 1967 pentazocine was released by the American Food and Drug Administration; however, at very high doses some incidence of psychomimetic activity was observed. More recent investigations have demonstrated that, parenterally, the respiratory depression caused by pentazocine is equal to that shown by morphine,[42] and also the absence of addictive properties has been questioned.[43] Prolonged administration of pentazocine produces dependence like morphine.

[38] L. Lasagna, T. J. DeKornfeld, and J. W. Pearson, *J. Pharmacol. Exp. Therap.*, 1964, **144**, 12.
[39] W. R. Martin, H. F. Fraser, C. W. Gorodetzky, and D. E. Rosenberg, *J. Pharmacol.*, 1965, **150**, 426.
[40] W. R. Martin, C. W. Gorodetzky, and T. K. McClane, *Pharmacologist*, 1965, **7**, 163.
[41] W. R. Martin, C. W. Gorodetzky, and T. K. McClane, *Clin. Pharmacol. Therap.*, 1966, **7**, 455.
[42] J. W. Belleville and W. H. Forrest, *Clin. Pharmacol. Therap.*, 1968, **9**, 142.
[43] W. Keup, *Diseases Nervous Syst.*, 1968, **29**, 599.

It was concluded that pentazocine has an abuse potential which, nevertheless, is inferior to that of morphine.[44]

A number of additional derivatives of pentazocine have been synthesised and pharmacologically tested, but these compounds have not shown any advantages over the parent compound.[45]

Oripavine and its Analogues. Oripavine analogues are chemically closer to genuine morphine alkaloids than the benzomorphans and their antagonistically acting derivatives, since they are obtained directly from the opium alkaloid, thebaine. The first observation on the addition of dienophiles to the conjugated double bond system of thebaine (27) was made by Sandermann[46] and by Schoepf *et al.*[47] Whereas Schoepf's paper is purely theoretical, Sandermann, albeit without concrete proposals, points to the possibility of using such addition products for pharmaceutical purposes. Analgetic activity of such addition compounds was first observed by Bentley in 1956,[48] but the recognition of the great potential of Diels–Alder addition products of thebaine and similarly constructed alkaloids probably dates from 1963.[49] By addition of $\alpha\beta$-unsaturated ketones to thebaine, a number of ketones derived from tetrahydro-6,14-*endo*-etheno-thebaine (28) could be obtained. Reaction of (28) with Grignard reagents gave tertiary alcohols of the general formula (29).



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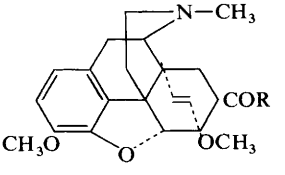

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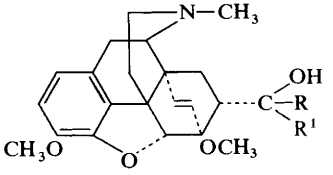


(29)

[44] D. R. Jasinski, W. R. Martin, and R. D. Hoeldtke, *Clin. Pharmacol. Therap.*, 1970, **11**, 385.

[45] K. Kanematsu, R. T. Parfitt, A. E. Jacobson, J. H. Ager, and E. L. May, *J. Amer. Chem. Soc.*, 1968, **90**, 1064; M. May, L. Czoncha, D. R. Garrison, and D. J. Triggle, *J. Pharm. Sci.*, 1968, **57**, 884.

[46] W. Sandermann, *Ber.*, 1938, **71**, 648.

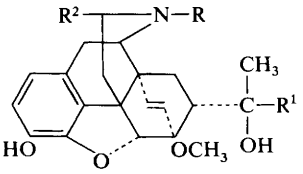
[47] Cl. Schoepf, K. von Gottberg, and W. Petri, *Annalen*, 1938, **536**, 216.

[48] K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1956, 1863.

[49] K. W. Bentley and R. A. Hardy, *Proc. Chem. Soc.*, 1963, 220; *Endeavour*, 1964, **23**, 97.

Compounds of the type (29) have analgetic activities ranging from the barely detectable to the high level of almost 10,000 times that of morphine, when determined by the subcutaneous route in rats (tail pressure method), and these activities have been confirmed in other animals. Reduction of the 6,14-*endo*-etheno-bridge produces the 6,14-*endo*-ethano-compounds, with only a slight change in analgetic activity. The most potent analgetics are found in the phenolic series, prepared by alkaline demethylation of the corresponding 3-methoxy compound, or by other means.

In recent years, Bentley and his colleagues[50] have published a series of remarkable papers and a number of patents have been granted. The most interesting compound of this series is etorphine [M99 (30; R = CH_3, R^1 = n-C_3H_7, R^2 = H)] the pharmacologic properties of which have been studied extensively.[51]



(30)

Depending on the test system used, etorphine proved to be 1000—80 000 times more potent than morphine. In a later paper,[52] dissociation of analgesic and respiratory depressant properties is claimed. With etorphine at equi-analgetic dose levels (which is a better way of comparison than with absolute weights[53]), respiratory depression is of greater prominence than with morphine.

In the light of earlier experience, the *N*-methyl group of etorphine has been replaced by allyl, n-propyl, n-pentyl, or cyclopropylmethyl groups. The allyl compound (30; R = allyl, R^1 = n-propyl, R^2 = H) seems to be a potent, morphine-like analgetic without antagonistic properties, but possessing good separation of analgetic from respiratory depressant properties.[52] The *N*-cyclopropylmethyl compound is a potent antagonist, but clinical investigations have produced a high incidence of side-effects. The cyclohexyl compound (30; R = methyl, R^1 = cyclohexyl, R^2 = H) is *ca.* 1000 times more active than morphine.[54] If the position *ortho* to the *N*-methyl is substituted by an additional methyl group

[50] K. W. Bentley, *J. Amer. Chem. Soc.*, 1967, **89**, 3267–3321 (6 papers); *J. Chem. Soc.* (*C*), 1969, 826, 2225–2242 (7 papers), 2385, 2569; *ibid.*, 1970, 560; *J. Medicin. Chem.*, 1970, **13**, 525.

[51] G. F. Blane, A. L. Boura, A. F. Fitzgerald, and R. E. Lister, *Brit. J. Pharmacol.*, 1967, **30**, 11; G. F. Blane, *J. Pharm. Pharmacol.*, 1967, **19**, 781.

[52] G. F. Blane, A. L. Boura, E. C. Leach, W. D. Gray, and A. C. Osterberg, *J. Pharmacol.*, 1968, **20**, 796.

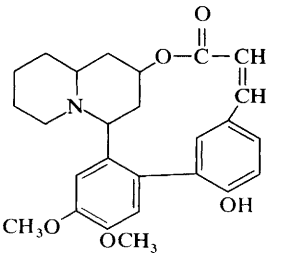
[53] See B. J. Pleuvry and J. M. Rees, *J. Pharm. Pharmacol.*, 1969, **21**, 814.

[54] L. Leadbeater and D. R. Davies, *Biochem. Pharmacol.*, 1968, **17**, 219.

(30; R = methyl, R^1 = cyclohexyl, R^2 = methyl) the antitussive activity is strongly enhanced, whereas the analgetic power is diminished.[55]

In this most interesting series of papers a great number of oripavine derivatives have been prepared and screened and it has been demonstrated that the analgetic potency of morphine can be increased by an unprecedented degree. Also, dissociation of the morphine effects has been obtained, which may go beyond that which has been reached with other morphine derivatives. The question of addiction, which is of paramount importance with such highly active compounds, still seems to be unsolved. Little has been published on this aspect yet and, in general, clinical reports are still scarce.

Anti-inflammatory Compounds.—Claims for anti-inflammatory activity of alkaloids appear in the literature from time to time, but in view of the difficulties connected with the testing of such compounds, positive results should be viewed with caution. Recently it has been stated that cryogenine from *Heimia salicifolia* (Lythraceae)[56] has anti-inflammatory activity. Lythraceae have been investigated broadly during recent years, probably because of an early claim that these alkaloids have hallucinogenic properties.[57] The structure (31) has been proposed for cryogenine.[58]



(31)

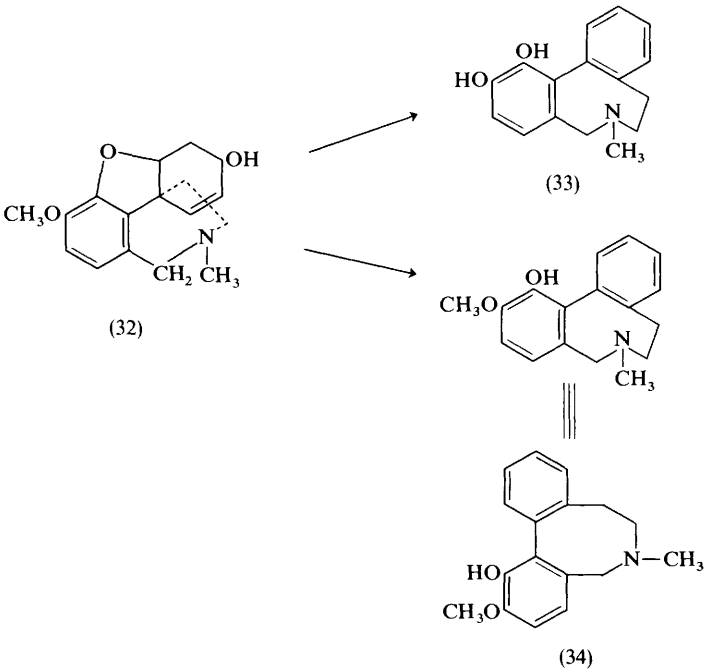
4 Cardiovascular Drugs: Antihypertensive Alkaloids

The use of reserpine, rescinnamine, and deserpidine as mild antihypertensives, mostly in combinations, has become a standard treatment of today. The search for additional antihypertensive plant alkaloids which set in after the discovery of reserpine has not yielded any great results. Some extracts or crystalline material

[55] A. L. A. Boura, D. I. Haddlesey, E. J. R. Harry, J. W. Lewis, and P. A. Mayor, *J. Pharm. Pharmacol.*, 1968, **20**, 961.
[56] H. R. Kaplan, R. E. Wolke, and M. H. Malone, *J. Pharm. Sci.*, 1967, **56**, 1385.
[57] R. C. Robichaud, M. H. Malone, and A. E. Schwarting, *Arch. Internat. Pharmacodyn.*, 1964, **150**, 220.
[58] A. Rother, H. G. Appel, J. M. Kiely, A. E. Schwarting, and J. M. Bobbitt, *Lloydia*, 1965, **28**, 90; A. Rother and A. E. Schwarting, *Chem. Comm.*, 1969, 1411.

proved to be hypotensive, but no clinically useful preparations resulted.[59] Modifications of the reserpine molecule and synthetic model compounds, prepared in great numbers, were mostly devoid of antihypertensive effects.[60]

It is difficult to judge to what extent apogalanthamine [Apotamine, (33)] and apogalanthamine monomethyl ether [Apochlorine, (34)], derivatives of the phenanthridine alkaloid galanthamine (32), are used clinically in Russia. Both (33) and (34) are obtained from (32) by treatment with acids:[61]



Apochlorine was given to rabbits, cats, and dogs intravenously and orally, and it is claimed to have about the same antihypertensive potency as reserpine.[62]

Another antihypertensive alkaloid, whose use is apparently favoured in Russia, is vincamine (35) from *Vinca minor*, which was first described in 1953.[63]

[59] See *e.g.*, G. B. Singh, M. L. Sharma, and B. J. Ghatak, *Indian J. Exp. Biol.*, 1969, **7**, 144; M. L. Sharma, G. B. Singh, and B. J. Ghatak, *ibid.*, 1967, **5**, 149.

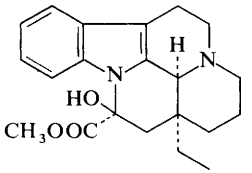
[60] E. Schlittler and H. J. Bein, in 'Antihypertensive Agents,' ed. E. Schlittler, Academic Press, New York–London, 1967, pp. 191—221.

[61] A. Abdusamatov, K. Abduazimov, and S. Y. Yunusov, *Khim. prirod. Soedinenii*, 1969, **5**, 194; 510; (*Chem. Abs.*, 1969, **71**, 128 624*q*).

[62] K. U. Aliev, I. K. Kamilov, and U. B. Zakirov, *Doklady Akad. Nauk Uzbek S.S.R.*, 1964, **21**, 50 (*Chem. Abs.*, 1965, **62**, 13 725); K. Nadzimutdinov, I. K. Kamilov, and U. B. Zakirov, *ibid.*, 1965, **22**, 32 (*Chem. Abs.*, 1966, **64**, 8807); for clinical studies see T. A. Levina and A. I. Romanovskaya, *Akad. Nauk. Uz. S.S.R.*, 1966, 77 (*Chem. Abs.*, 1967, **67**, 62 938*d*).

[63] E. Schlittler and A. Furlenmeier, *Helv. Chim. Acta*, 1953, **36**, 2017.

Although its hypotensive activity was noticed at that time, it was thought to be insufficient for any practical purposes. Vincamine is being extracted on a tech-



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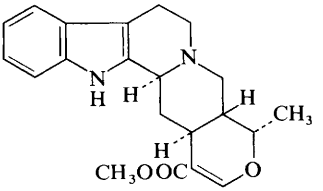

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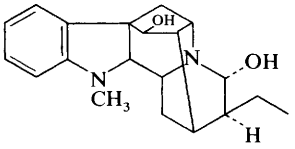


(37) (≡44)

nical scale in Hungary today[64] and it is apparently used as an antihypertensive drug in Eastern countries. Its pharmacological literature is mostly Hungarian, but is available from Chemical Abstracts.[65] Vincamine given intramuscularly to humans with cerebral sclerosis improved their EEC, indicating improved cerebral circulation.[66] Vincamine has been introduced under several trade names as a preparation for increasing cerebral and coronary circulation.

Similar claims are also made for ajmalicine (raubasine) (36), an alkaloid obtained from many *Rauwolfia* species.[67] Technically, ajmalicine is obtained by catalytic hydrogenation of serpentine, a quaternary alkaloid which occurs plentifully in most *Rauwolfia* species. Ajmalicine has recently been introduced commercially in several countries.

More interesting is the pharmacology of ajmaline (37), which is available in large quantities as a by-product of the reserpine extraction. Detailed pharmacological studies seemed to be more than justified because reserpine did not possess all the pharmacological effects of crude *Rauwolfia* extracts. Ajmaline was compared with quinidine[68] and studied clinically in cardiac arrhythmias,

[64] Hung. P. 147 282, July 1960 and Hung. P. 151 295, March 1964.

[65] See also Raymond-Hamet, *Compt. rend. Soc. Biol.*, 1954, **148**, 1082; L. Szporny and K. Szasz, *Arch. Exp. Path. Pharmakol.*, 1959, **236**, 296; Z. Szabo and Z. Nagy, *Arzneimittel-Forsch.*, 1960, **10**, 811; L. Szporny and P. Gorog, *Arch. Int. Pharmacodyn.*, 1962, **138**, 451.

[66] M. Foldi, F. Obal, and G. Szeghy, *Med. Welt*, 1965, **37**, 2122; F. Solti, *Therapia Hungarica*, 1965, **13**, 101.

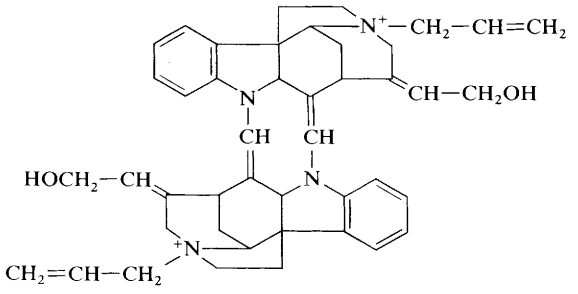
[67] K. Dietmann, *Arzneimittel-Forsch.*, 1967, **17**, 969; M. Laubie and J. C. Douarec, *ibid.*, 1969, **19**, 1820.

[68] G. Kuschinsky and H. Reuter, *Arch. Exp. Path. Pharmakol.*, 1961, **242**, 17.

with somewhat ambiguous results. In general, European clinicians have been enthusiastic about the effects of ajmaline,[69] whereas American investigators have mostly shied away from ajmaline because of its toxicity. Ajmaline, alone or in combination, has been introduced in many European countries. Also simple derivatives of ajmaline have been prepared with the hope of diminishing its toxicity,[70] but it is unknown whether any such derivative of ajmaline has been commercialised.

5 Tubo- and Calabash-curare

Although crystalline tubocurare preparations have been used therapeutically for many years, calabash-curare alkaloids have attracted more interest recently. Toxiferine I (Ro 4-2906) and *NN'*-diallylbisnortoxiferine chloride (Ro 4-3816) have been investigated pharmacologically and clinically in great detail.[71] *NN'*-Diallylbisnortoxiferine [(38), Ro 4-3816] was introduced commercially in 1964, under the trade name Alloferine as a short acting muscular relaxant. Nortoxiferine (39), originally extracted in quaternised form from calabash-curare or from *Strychnos toxifera* (Loganiaceae), is now prepared semi-synthetically by dimerisation of the Wieland–Gumlich aldehyde (40) (obtained from strychnine) to (39)

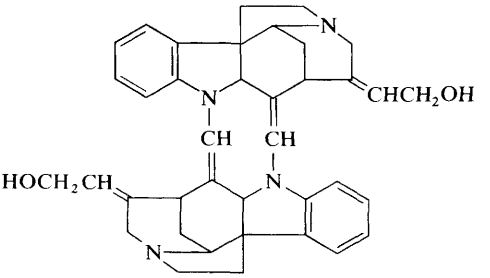


(38)

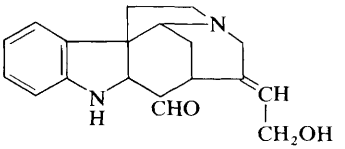
[69] C. Mela, *Fitoterapia*, 1967, **38**, 2; G. Foster and M. Holzmann, *Schweiz. Med. Wschr.*, 1967, **97**, 185 216; see also 'Heart Rhythm Disturbances,' ed. M. Holzmann (in German), Schattauer Verlag, Stuttgart–New York, 1968, and H. Kleinsorge and E. Voelkner, 'Medicamentum,' 1962, p. 261.

[70] C. Capra, *Farmaco (Pavia) Ed. sci.*, 1964, **19**, 865; A. Bonati and C. Capra, *Fitoterapia*, 1967, **38**, 22; E. I. Gendenshtein, *Byull. Eksp. Biol. Med.*, 1969, **67**, 60 (*Chem. Abs.*, 1969, **70**, 1923*f*).

[71] Ro 4-2906: R. Seeger, *Arch. Exp. Path. Pharmakol.*, 1963, **244**, 493; P. G. Waser and P. Harbeck, *Anaethesist*, 1959, **8**, 193; R. Seeger, *ibid.*, 1961, **10**, 129, 325; W. Huegin and P. Kissling, *ibid.*, 1961, **10**, 137.
Ro 4-3816: H. P. Baechtold, F. Fornosari, and A. Huerlimann, *Helv. Physiol. Pharmacol. Acta*, 1964, **22**, 70; A. Huerlimann and H. P. Baechtold, *Bull. Schweiz. Akad. Med. Wiss.*, 1967, **22**, 511; R. Seeger, F. Ahnefeld, and E. Hauenschild, *Anaethesist*, 1962, **11**, 37; P. G. Waser and P. Harbeck, *ibid.*, 1962, **11**, 33; A. R. Hunger, *Brit. J. Anaesthesia*, 1964, **36**, 466.

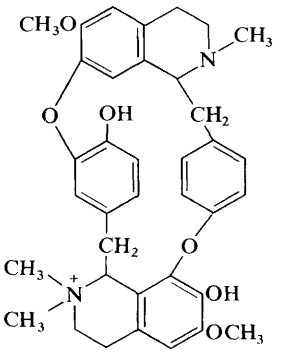


(39)



(40)

and subsequent quaternisation with allyl bromide[72] to (38). Absence of blood-pressure lowering and bronchoconstriction, present in impure calabash preparations, makes derivatives of toxiferine suitable for human therapy.[73] They are somewhat more potent than crystalline tubocurare preparations [*e.g. d*-tubocurarine chloride (40a)],[74] but their duration of action seems to be shorter than the latter, which is an advantage for human use. The initial dose of Alloferine



(40a)

[72] For a review see A. Battersby and H. F. Hodson in 'The Alkaloids: Chemistry and Physiology', ed. R. H. F. Manske, Academic Press, New York–London, 1965, **8**, 515—579; *ibid.*, 1968, **11**, 189—204.

[73] P. G. Waser, *Bull. Schweiz. Akad. Med. Wiss.*, 1967, **22**, 486.

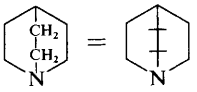
[74] See R. Seeger (1961) under ref. 1; A. J. Everett, L. A. Lowe, and S. Wilkinson, *Chem. Comm.*, 1970, 1020.

in humans is *ca.* 40—50 $\mu g\ kg^{-1}$ and the maintenance dose *ca.* 15 $\mu g\ kg^{-1}$. The duration of action depends on the dose, but it can last 20—40 min.

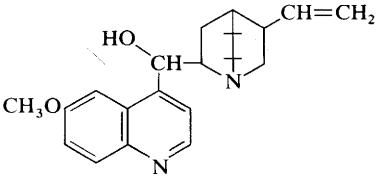
Much synthetic work has been done in the field of the tubocurare alkaloids, and a Russian group under O. N. Tolkachev and N. A. Preobrazhenskii[75] has been very active. It is, however, not clear whether any new clinically useful muscular relaxants have been developed from this research.

6 Quinuclidines and Iso-quinuclidines

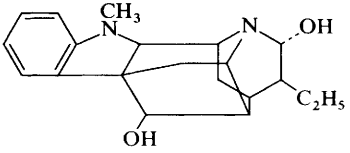
The quinuclidines (41) and, to a lesser extent, the iso-quinuclidines (42) have attracted considerable interest since they are themselves parts of alkaloids. The quinuclidine system is contained in the *Cinchona* alkaloids (43), in ajmaline (44) from *Rauwolfia* spp., and in macusine (45) obtained from *Strychnos* spp. The iso-quinuclidine ring structure occurs in the *Iboga* alkaloids (46):



(41)

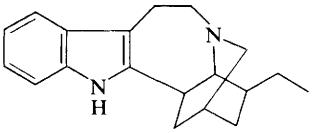


(43)

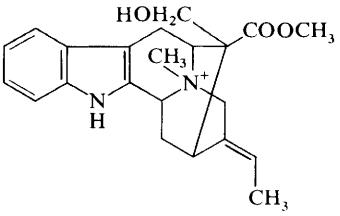


(44) (≡ 37)

(42)



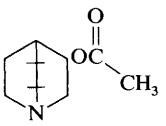
(46)



(45)

[75] O. N. Tolkachev, *J. Sci. Ind. Res. India*, 1967, **26**, 209 (*Chem. Abs.*, 1967, **67**, 116 993*p*).

This field has been explored exclusively by Russian chemists and biologists under the leadership of M. V. Rubtsov and M. D. Mashkovsky.[76] The following drugs have been developed: Aceclidine (47), Aprolidine (48), Oxylidine (49), Diochine (50), and Qualidile (51).



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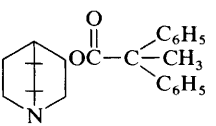

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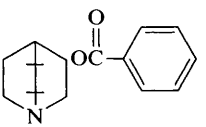
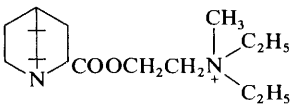
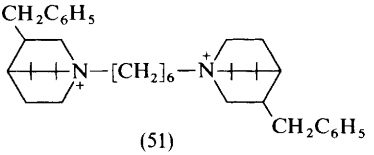


(49)



(50)



(51)

Aceclidine is mostly used in ophthalmology for constriction of the pupil and reduction of intraocular pressure in glaucoma.[77] Oxylidine is being used as a tranquilliser in patients with neurotic states and early states of hypertension. It is also recommended for the treatment of cerebral atherosclerosis. Its oral dose is 0.02—0.5 g. Qualidile is a curare-like drug used in general anaesthesia. The preparation is injected intravenously; at a dose of 1 mg kg^{-1}, muscle relaxation lasts for 10 minutes, slight inhibition of respiration being observed. A dose of 2 mg kg^{-1} produces complete relaxation of the skeletal muscles, accompanied by apnoea. In spite of the fact that the review[76] is well documented, it is difficult to form an idea about the clinical merits of these compounds. Some clinical information has been published recently;[78] a comparison of Qualidile with *NN'*-diallylbisnortoxiferine or tubocurarine chlorides (*loc. cit.*) would be of special interest.

Some other claims made for these quinuclidine derivatives are anti-Parkinson activity, antiarrhythmic and local anaesthetic effects, antimalarial activity, and central stimulation, but none of these properties has led to a therapeutic preparation.

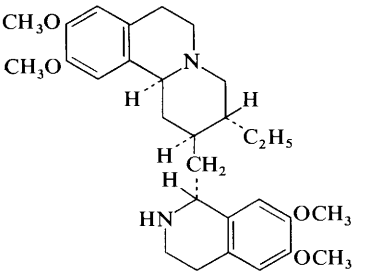
Iso-quinuclidine derivatives have not been investigated in detail. In 1958, a number of iso-quinuclidines were screened without success[79] and later investigations did not reveal any activities suitable for human therapy.

[76] M. D. Mashkovsky and L. N. Yakhontov in 'Progress in Drug Research', ed. E. Jucker, Birkhäuser Verlag, Basel–Stuttgart, 1969, **13**, 293—339.
[77] M. D. Mashkovsky and K. A. Zaitseva, *Farmakol. i Toksikol.*, 1962, **25**, 32.
[78] T. A. Levina, *Tr. S'zenda Ter. Ukr. S.S.R.*, 1965 (publ. 1967), 600 (*Chem. Abs.*, 1969, **70**, 46 129*x*).
[79] L. H. Werner and S. Ricca, *J. Amer. Chem. Soc.*, 1958, **80**, 2733.

7 Chemotherapy of Amoebiasis: 2-Dehydroemetine

Emetine (52) has been used for the treatment of amoebiasis since 1912.[80] In spite of its unquestionable activity, emetine proved to be quite toxic and often curative doses were close to the range of toxicity. For this reason molecular modification of the emetine structure seemed to have some prospec of success. In 1950, the first total synthesis of emetine was announced[81] and was followed by a number of additional syntheses. These achievements made possible the syntheses of stereoisomers of emetine and of other synthetic derivatives. All stereoisomers synthesised were less active than the natural (−)-emetine and most of the compounds were also less toxic.[82]

The most promising emetine derivative proved to be 2-dehydroemetine [DHE, (53)] which, from the synthetic point of view, has the added advantage of possessing only two asymmetric carbon atoms, whereas emetine has four. (±)2-Dehydro-



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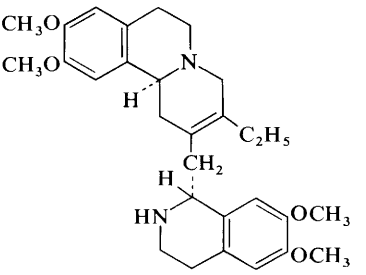


(53)

emetine, which cannot be obtained from emetine by removal of two hydrogen atoms, was first synthesised in 1959[83] and was found to be about 6 times as active as emetine in rats infected with *Endamoeba histolytica.* It was generally agreed that 2-dehydroemetine was also less toxic than emetine.[84] Early clinical trials were initiated in 1960[85] and confirmed the higher activity and lower

[80] R. B. Vedder, *J. Trop. Med.*, 1912, **15**, 313.

[81] R. P. Evstigneeva, R. S. Livshits, L. I. Zahtarkin, M. S. Bainova, and N. A. Preobrazhenskii, *Doklady Akad. Nauk S.S.S.R.*, 1950, **50**, 539; R. P. Evstigneeva and N. A. Preobrazhenskii, *Tetrahedron*, 1958, **4**, 223.

[82] M. Barash, J. M. Osbond, and J. C. Wickens, *J. Chem. Soc.*, 1959, 3530; A. Brossi, Z. Brener, J. Pellegrino, H. Stohler, and J. R. Frey, *Experientia*, 1960, **16**, 64; D. E. Clark, R. F. K. Meredith, A. C. Ritchie, and T. Walker, *J. Chem. Soc.*, 1962, 2490; for reviews see C. Viel and P. Rumpf, *Bull. Soc. chim. France*, 1962, 2235, and H. T. Openshaw in 'Chemistry of the Alkaloids', ed. S. W. Pelletier, Van Nostrand Reinhold Co., New York–London, 1970, pp. 85–115.

[83] A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Wuersch, F. Schneider, and O. Schnider, *Helv. Chim. Acta*, 1959, **42**, 772.

[84] M. L. Chatterjee and M. S. De, *Bull. Calcutta School Trop. Med.*, 1963, **11**, 16 (*Chem. Abs.*, 1963, **59**, 12 057); J. Herrero, A. Brossi, M. Faust, and J. R. Frey, *Ann. Biochem. Exp. Med.*, 1960, suppl. **20**, 475 (*Chem. Abs.*, 1963, **59**, 3243).

[85] F. Blanc, Y. Nosny, M. Armengaud, M. Sankale, M. Martin, and G. Charnot, *Presse Med.*, 1961, **69**, 1548.

toxicity of dehydroemetine. All four possible optically active forms of 2-dehydroemetine were prepared by a Roche group. Of these four stereoisomers, only (−)-2-dehydroemetine proved to possess the expected amoebicidal activity and acute toxicity, whereas the (+) isomer and both 2-dehydroisoemetines were inactive.[86] A second approach to 2-dehydroemetine has been described recently.[87]

Clinicians had generally agreed that 2-dehydroemetine was less toxic than emetine itself,[88] but there has been a change of opinion within the last few years. Chronic toxicity experiments have demonstrated that natural emetine and 2-dehydroemetine have about the same toxicity, and in caecal infections with *E. histolytica* in the rat they also have similar activity.[89]

Both natural emetine and 2-dehydroemetine can be synthesised by commercially feasible processes, but in countries like India emetine is still extracted from plant material. 2-Dehydroemetine has not been able to replace emetine and today, as far as is known, it is being sold by only one pharmaceutical company.

8 Alkaloids as Tumour Inhibitors

Within the last 10 years a great number of plants have been screened for antitumour active alkaloids. The two major groups involved in this search were the National Cancer Institute and a group of chemists and biologists at Eli Lilly and Co. Crude extracts and crystalline alkaloids were screened *in vitro* (cell cultures) and *in vivo* against sarcoma 180, Walker 256 intramuscular carcinosarcoma, Eagle's K.B. strain of human carcinoma of the nasopharynx, Lewis lung carcinoma, *etc.* The tests, which were reproducible, were made under standard conditions set up by the C.C.N.S.C. (Cancer Chemotherapy National Service Centre).

Search for Anti-tumour Alkaloids Undertaken by the Lilly Group.—The Lilly group's interest seems to have narrowed down to a few botanical genera and should therefore be discussed first. The most important genus of this group is *Catharanthus roseus* G. Don (Apocynaceae), formerly called *Vinca rosea* L., an everblooming pantropical shrub. Its oral hypoglycemic activity[90] was never confirmed, but a chance observation, made independently by two research groups, demonstrated the anti-tumour activity of *Catharanthus roseus* extracts.

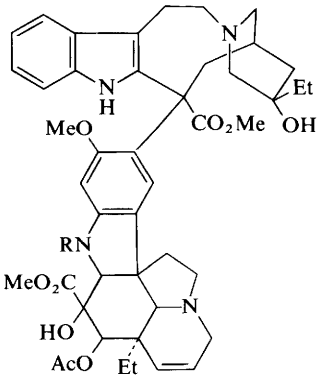
A Canadian group, by fractionation of crude extracts, obtained vincaleukoblastine (vinblastine, VLB), $C_{46}H_{58}N_4O_9$, an alkaloid capable of producing severe leukopenia in rats.[91]

[86] A. Brossi and F. Burkhardt, *Experientia*, 1962, **18**, 211; A. Brossi, M. Baumann, F. Burkhardt, R. Richle, and J. R. Frey, *Helv. Chim. Acta*, 1962, **45**, 2219.
[87] N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 94.
[88] See *e.g.*, G. Wolfe in 'Progress in Drug Research', ed. E. Jucker, Birkhäuser Verlag, Basel–Stuttgart, 1965, **8**, p. 19 ff.
[89] P. Johnson and R. A. Neal, *Ann. Trop. Med. Parasitol.*, 1968, **62**, 455.
[90] F. Garcia, *Proc. 8th Pacific Sci. Congr., Nat. Council Res. Philippines*, 1954, IV, 182.
[91] C. T. Beer, *Brit. Empire Cancer Conf., 33rd Annual Rep.*, 1955, 487; J. H. Cutts, C. T. Beer, and R. L. Noble, *Rev. Canad. Biol.*, 1957, **16**, 476; R. L. Noble, C. T. Beer, and J. H. Cutts, *Ann. N.Y. Acad. Sci.*, 1958, **76**, 882; J. H. Cutts, C. T. Beer, and R. L. Noble, *Cancer Res.*, 1960, **20**, 1023.

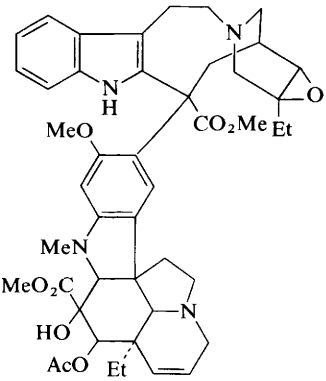
The Eli Lilly team[92] isolated from a Madagascan *Catharanthus roseus* VLB-sulphate, as well as the new alkaloid leurosine (vinleurosine, VLR), $C_{46}H_{58}N_4O_9$, which is chemically closely related to VLB. Leurosine has also been isolated from *Catharanthus lanceus* Pich.[93]

Four additional anti-tumour active alkaloids, leurosidine (vinrosidine, VRD) and leurocristine (vincristine, VCR), $C_{46}H_{56}N_4O_{10}$,[94] as well as leurosivine and rovidine,[95] were later isolated. Owing to the anti-tumour activity of the *Catharanthus* alkaloids and the antihypertensive activity of vincamine, from *Vinca minor*, this group attracted much attention in the mid-1960s. In June 1964, a symposium on the chemistry and biological activity of *Catharanthus*, *Vinca*, and related alkaloids took place in Pittsburgh within the frame of the Fifth Annual Meeting of the American Society of Pharmacognosy. The December issue of 'Lloydia'[96] contains all the papers presented, and thus the status of the *Catharanthus* and *Vinca* research as of 1964 is clearly defined. A more recent, very valuable review is 'Anti-tumoral Effects of *Vinca rosea* Alkaloids'.[97]

For the two dimeric alkaloids VLB and VCR the formulae (54) have been elaborated.



(54); R = CH_3: Vincaleukoblastine or vinblastine
R = CHO: Leurocristine or vincristine



(55)

[92] G. H. Svoboda, *J. Amer. Pharm. Ass., Sci. Ed.*, 1958, **47**, 834; I. S. Johnson, H. F. Wright, and G. H. Svoboda, *J. Lab. Clin. Med.*, 1959, **54**, 830; I. S. Johnson, H. F. Wright, G. H. Svoboda, and J. Vlantis, *Cancer Res.*, 1960, **20**, 1016; G. H. Svoboda, N. Neuss, and M. Gorman, *J. Amer. Pharm. Ass., Sci. Ed.*, 1959, **48**, 659.

[93] R. N. Farnsworth, W. D. Loub, and R. N. Blomster, *J. Pharm. Sci.*, 1963, **52**, 1114; W. D. Loub, N. R. Farnsworth, R. N. Blomster, and W. W. Brown, *Lloydia*, 1964, **27**, 470.

[94] G. H. Svoboda, *Lloydia*, 1961, **24**, 173; *ibid.*, 1963, **26**, 141.

[95] G. H. Svoboda, A. T. Oliver, and D. R. Bedwell, *Lloydia*, 1963, **26**, 141; G. H. Svoboda and A. J. Barnes, jun., *J. Pharm. Sci.*, 1964, **53**, 1227.

[96] *Lloydia*, 1964, **27**, 275–485.

[97] Proc. First Symp. of the European Group of Anti-cancer Therap., ed. S. Garattini and E. M. Sproston, Excerpta Medica Foundation, 1966, no. 166, 197 pp.

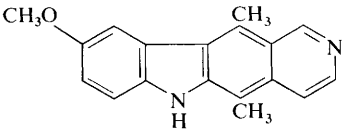
The latest structure for VLR (leurosine, vinleurosine) (55) was obtained primarily by analytical methods like i.r., n.m.r., and mass spectroscopy.[98] No structure has yet been proposed for VRD (leurosidine, vinrosidine), leurosivine, or rovidine. An additional number of dimeric indole bases (24 out of the total of 72 alkaloids isolated) have been obtained from *Catharanthus*, but they seem to be devoid of anti-tumour activity.

Since the yields of active dimeric alkaloids from *Catharanthus roseus* is the lowest of any medicinally useful compounds (yield of VCR = 3×10^{-4}%), material for studies of structure–activity relations has been scarce. Nevertheless, such studies were performed with VLB[99] and it has been claimed that some of the products of molecular modification are more active in animal tests than VLB itself.[97]

VLB and VCR have shown significant differences in their clinical activity against human neoplasm.[100] VLB is preferred in the treatment of Hodgkin's disease because of its better tolerance. VCR is superior to VLB in the treatment of lymphosarcoma, but this is in part counterbalanced by its greater toxicity.[101] The combined use of VLB and VCR has also been discussed.[102] Dihydro-VLB is much less toxic to animals, and its anti-tumour activity is lower than that of VLB, but the response differs from VLB.[103]

Eli Lilly introduced VLB (Velban ^{T}) as an anti-cancer agent *ca.* 1961. It is effective in treating chorioepithelioma, Hodgkin's disease, and other lymphomas and, in addition, a number of beneficial results have been obtained in treating breast cancer. VCR (Oncovin ^{T}) is used to treat leukaemia in children.

From *Ochrosia maculata* (*O. borbonica*), (Apocyn.), 9-methoxyellipticine (56) was isolated[104] as the substance responsible for the anti-tumour properties of *Ochrosia* extracts. (56) is active against L-1210 leukaemia in mice resistant to 6-mercaptopurine at 250 mg kg^{-1} p.o.[105] Other closely related alkaloids, such as olivacine (56a), show similar activities.



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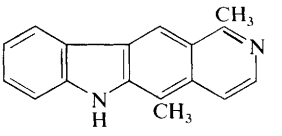


(56a)

[98] D. J. Abraham and R. N. Farnsworth, *J. Pharm. Sci.*, 1969, **58**, 694.

[99] *e.g.*, W. W. Hargrove, *Lloydia*, 1964, **27**, 340: see also G. H. Svoboda (ref. 97) and I. S. Johnson, W. W. Hargrove, P. N. Harris, H. F. Wright, [illegible] B. Boder, *Cancer Res.*, 1966, **26**, 2431.

[100] I. S. Johnson, J. G. Armstrong, M. Gorman, and [illegible] P. [illegible]tt, *Cancer Res.*, 1963, **23**, 1390.

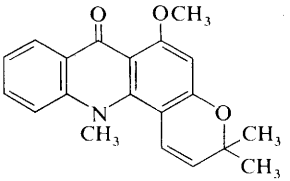
[101] E. Frey, *Lloydia*, 1964, **27**, 364.

[102] G. Cardinali and G. Cardinali, *Chemotherapia*, 1967, **12**, 226.

[103] R. L. Noble, C. T. Beer, and R. McIntyre, *Cancer (Philadelphia)*, 1967, **20**, 885.

[104] G. H. Svoboda, G. A. Poore, and L. M. Montfort, *J. Pharm. Sci.*, 1968, **57**, 1720.

[105] C. T. Hardesty and N. A. Chaney, *Proc. Amer. Ass. Cancer Res.*, 1970, **11**, 34, abstr. 132.



(57)

Acronycine (57), isolated in the Lilly laboratories from different *Acronychia* spp. (Rutaceae), has shown the broadest experimental tumour activity of any alkaloid studied. It was first isolated from *Acronychia baueri*.[106] Its activity against C-1498 myelogenous leukaemia, X-5563 plasma cell myeloma, and adenocarcinoma 755 was found by the Lilly group.[107] Acronycine has been obtained by different syntheses;[108] however, no evidence for clinical trials with acronycine has yet been found in the literature.

Search for Anti-tumour Alkaloids, Sponsored by N.C.I.—The National Cancer Institute (N.C.I.), in collaboration with the U.S.D.A. (U.S. Department of Agriculture), organised a plant collection programme and by 1966 it had collected about 11 000 random samples of plants from some 5000 species. Other plant collectors associated with this programme are the University of Arizona and the Commonwealth Scientific and Industrial Research Organisation (C.S.I.R.O.) of Melbourne, Australia. The plant material is prescreened for anti-tumour activity and the positive samples are then distributed between a number of American research organisations.[109] The most important *in vivo* tumours used for testing in the standardised N.C.I. programme are the Walker 256 carcinosarcoma in rats. Up to September 1966, the N.C.I. had published data on 10 237 plant extracts tested mostly in sarcoma 180, carcinoma 755, leukaemia L-1210, and K.B. cell culture.

So far, a group of chemists under S. M. Kupchan at the University of Virginia have been most active in collaborating with this N.C.I. scheme. In addition to many non-alkaloidal compounds, the alkaloids (58)—(62) have been isolated for which some anti-tumour activity is claimed.

Thalisidine (58) from *Thalictrum dasycarpum* (Ranunc.)[110] showed significant activity against the Walker carcinosarcoma in rats; solapalmitine (59) and sola-

[106] F. N. Lahey and W. C. Thomas, *Austral. J. Sci. Res.*, 1949, **2A**, 423; R. D. Brown, L. J. Drummond, F. N. Lahey, and W. C. Thomas, *ibid.*, 1949, **2A**, 622.

[107] G. H. Svoboda, *Lloydia*, 1966, **29**, 206; G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. A. Boder, *J. Pharm. Sci.*, 1966, **55**, 758; I. S. Johnson, G. H. Svoboda, G. A. Poore, and G. B. Boder, *Proc. Cancer Chemotherapy, Takeda Int. Conf. Osaka*, 1966 (publ. 1967), ed. A. Goldin, Maruzen Co. Ltd., Tokyo, 177 pp.

[108] J. R. Beck, R. N. Booher, A. C. Brown, R. Kwok, and A. Pohland, *J. Amer. Chem. Soc.*, 1967, **89**, 3934; *ibid.*, 1968, **90**, 4706; J. Hlubucek, E. Ritchie, and W. C. Taylor, *Chem. and Ind.*, 1969, 1809; *Austral. J. Chem.*, 1970, **23**, 1881.

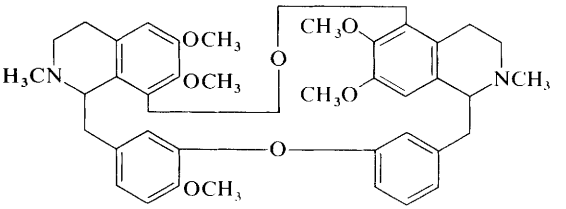
[109] *Chem. Eng. News*, 1966, Dec. 12th.

[110] S. M. Kupchan, T. H. Yang, G. S. Vasilikiotis, M. H. Barnes, and M. L. King, *J. Amer. Chem. Soc.*, 1967, **89**, 3075; *J. Org. Chem.*, 1969, **34**, 3884.

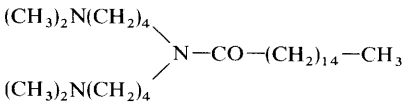
palmitenine (60) from *Solanum tripartitum* (Solanaceae)[111] showed significant activity against the Walker carcinosarcoma in rats; β-solamarine (61) from *Solanum dulcamara* (Solanac.) is a glyco-alkaloid built up from β-tomatidenol + 2L-rhamnose + 1D-glucose,[112] which showed anti-tumour activity against sarcoma 180 in mice; senecionine (62) and senecionine-*N*-oxide from *Senecio triangularis* (Compos.)[113] inhibit Walker carcinoma 256 tumour growth *in vivo*.

Monocrotaline (63) from *Crotalaria spectabilis* (Legum.)[114] is responsible for the activity of *Crotalaria* extracts against adenocarcinoma-755 in mice. Similar alkaloids have been screened for anti-tumour activity by other researchers;[115] in general, however, pyrrolizidine alkaloids have liver toxicity and it is questionable whether they can be used in chemotherapy. Furthermore, cissampareine (64) from *Cissampelos pareira* (Menisperm.)[116] and coronaridine (65) from *Ervatamia dichotoma* (Apocyn.)[117] have been investigated by the Kupchan group.

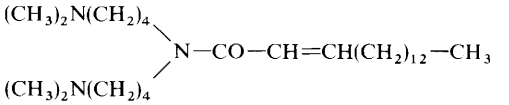
The alkaloid camptothecin (66) from *Camptotheca acuminata* (Nyssac.) has created much interest recently.[118] When tested against leukaemia L-1210 in mice



(58)



(59)



[111] S. M. Kupchan, A. P. Davies, S. J. Barboutis, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 1967, **89**, 5718; *J. Org. Chem.*, 1969, **34**, 3888.

[112] S. M. Kupchan, S. J. Barboutis, J. R. Knox, and C. A. Lau-Cam, *Science*, 1965, **150**, 1827.

[113] S. M. Kupchan and M. I. Suffness, *J. Pharm. Sci.*, 1967, **56**, 541.

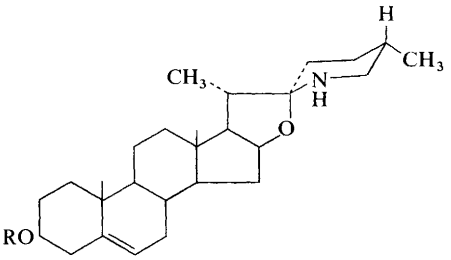
[114] S. M. Kupchan, R. W. Doskotch, and P. W. Vanevenhoven, *J. Pharm. Sci.*, 1964, **53**, 343.

[115] See *e.g.*, C. C. J. Culvenor, *J. Pharm. Sci.*, 1968, **57**, 1112; R. K. Sharma and P. Hebborn, *J. Medicin. Chem.*, 1968, **11**, 620.

[116] S. M. Kupchan, S. Kubota, E. Fujita, S. Kobayashi, H. J. Block, and S. A. Telang, *J. Amer. Chem. Soc.*, 1966, **88**, 4212.

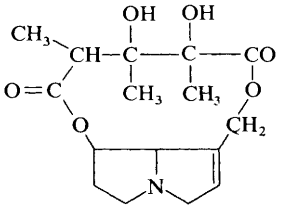
[117] S. M. Kupchan, A. Bright, and E. Macko, *J. Pharm. Sci.*, 1963, **52**, 598.

[118] M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, 1966, **88**, 3888.

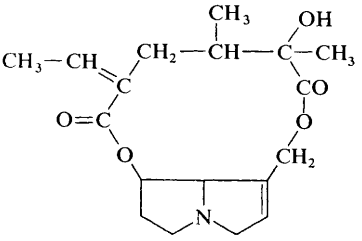


(61)

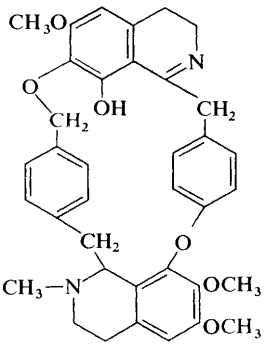
R = 2 L-rhamnose +
1 D-glucose



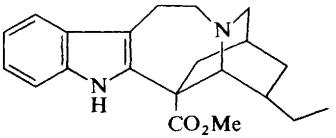
(62)

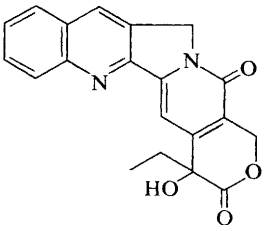


(63)



(64)





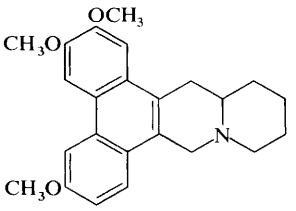
(66)

it gives life prolongation as high as 100% at 0.25—1.0 mg kg^{-1}, is also active against the Walker tumour, and shows moderate toxicity in K.B. cell culture. Also two minor alkaloids of *C. acuminata* possess anti-leukaemic activity.[119] Camptothecin is a neutral compound, which does not form stable salts with acids. Its constitution has been elucidated by high-resolution mass spectrography and *X*-ray analysis.[120]

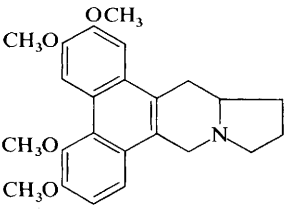
Synthetic approaches to the camptothecin ring system have been published recently;[121] for toxic effects of the camptothecin sodium salt see ref. 122. Clinical trials with (66)-Na salt have already been undertaken. Twelve patients with refractory metastatic solid tumours received 20 trials with this compound at 0.5—10.0 mg kg^{-1} *i.v.* In five patients there was more than 50% tumour reduction and improved liver functions in three others; duration of response was brief (about 6 weeks). Toxicity effects consisted of alopecia (33%), vomiting (33%), and cystitis (8%). The drug was relatively well tolerated at 7.5 mg kg^{-1} every two weeks or at 10 mg kg^{-1} every three weeks.[123]

A cytotoxic alkaloid from *Boehmeria cylindrica* (Urticaceae), active in cell cultures against Eagle's K.B. carcinoma of the nasopharynx, but inactive against sarcoma 180, adenocarcinoma 755, L-1210 leukaemia, and Walker carcinosarcoma, was identified as cryptopleurine (67).[124] (67) is a close relative of tylocrebrine (68), from *Tylophora crebrifolia* (Asclepiadaceae),[125] whose high activity against lymphoid leukaemia L-1210 in mice had been observed.[126]

Most of the alkaloids isolated from *Tylophora* which have a phenanthroindolizidine skeleton exhibit cytotoxic activity against HeLa cells, the position

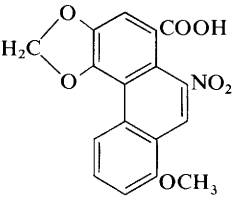


(67)



(68)

[119] M. C. Wani and M. E. Wall, *J. Org. Chem.*, 1969, **34**, 1364.
[120] See *e.g.*, *Chem. Eng. News*, 1966, July 11th.
[121] M. Shamma and L. Novak, *Tetrahedron*, 1969, **25**, 2275; J. A. Kepler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, 1969, **34**, 3853; M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Comm.*, 1970, 404.
[122] U. Schaeppi, D. A. Cooney, and R. D. Davis, U.S. Govt. Res. Develop. Rep., 1969, **69**, 46, 54 (*Chem. Abs.*, 1969, **71**, 105 030*k*).
[123] J. A. Gottlieb, A. M. Guarino, V. T. Oliverio, and J. D. Block, *Proc. Amer. Cancer Res.*, 1970, **11**, 31, abstr. 121.
[124] N. R. Farnsworth, N. K. Hart, S. R. Johns, J. A. Lamberton, and W. Messmer, *Austral. J. Chem.*, 1969, **22**, 1805.
[125] E. Gellert, T. R. Govindachari, M. V. Lakshmikantham, I. S. Ragade, R. Rudzats, and N. Viswanathan, *J. Chem. Soc.*, 1962, 1008.
[126] E. Gellert and R. Rudzats, *J. Medicin. Chem.*, 1964, **7**, 361.



(69)

of the methoxy-group being decisive for the anti-tumour potency. In this connection it is interesting to remember that anti-tumour activity has also been claimed for aristolochic acid (69) which contains a substituted phenanthrene as well as a nitro-group.[127]

For the tumour-inhibiting activity of amides from *Piper novaehollandiae* (Piperaceae) see ref. 128. Tumour-inhibiting extracts have also been obtained from *Brugueria* spp. (Rhizophoraceae), but it is not clear whether this activity is partly associated with tannins or with tannin-free compounds.[129]

Finally, the anti-tumour activity of colchicine and its derivatives should be remembered. However, this field has not been a very active one during recent years.

No conclusions as to any structure–activity relationship can be made in the field of tumour inhibitory alkaloids, in spite of the enormous amount of work that has been carried out. Structures and origin of alkaloids vary widely and it does not seem to be the prerogative of a few plant families to elaborate tumour inhibiting alkaloids. Two *Catharanthus* alkaloids and a few colchicine derivatives have become commercial products, but they certainly do not represent a final solution to the enormously complicated cancer problem.

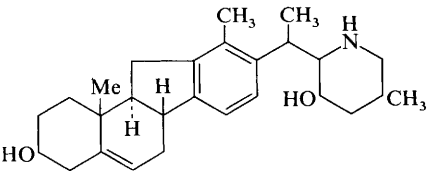
9 Teratogenesis Caused by Alkaloids

Occasionally alkaloids have been held responsible for teratogenesis in animals. However, such statements have been infrequent, with the exception of those concerning extracts from *Veratrum californicum* (Liliaceae). Congenital malformations (malformed or useless legs) in living new-born lambs were produced by maternal ingestion of *V. californicum* on the 14th day of gestation.[130] These lesions are probably caused by veratramine (70),[131] although it is difficult to understand why teratogenesis has not been observed with other *Veratrum* species in which veratramine occurs.

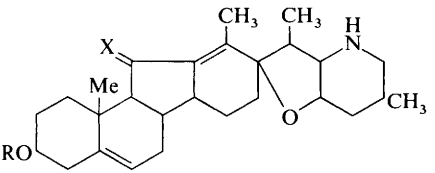
In addition to this general teratogenesis, extracts of *V. californicum* have some cyclopian effects for which the new alkaloid cyclopamine (71) and its 3-glucoside

[127] S. M. Kupchan and J. J. Merianos, *J. Org. Chem.*, 1968, **33**, 3735.
[128] J. W. Loder, A. Moorhouse, and G. B. Russel, *Austral. J. Chem.*, 1969, **22**, 1531.
[129] J. W. Loder and G. B. Russel, *Austral. J. Chem.*, 1969, **22**, 1271.
[130] R. F. Keeler and W. Binns, *Proc. Soc. Exp. Biol. Med.*, 1964, **116**, 123; 1967, **126**, 452.
[131] R. F. Keeler and W. Binns, *Proc. Soc. Exp. Biol. Med.*, 1966, **123**, 921.

(72) have been held responsible.[132] For cyclopamine the structure of an 11-deoxojervine [jervine = (73)] has been proposed.[133]



(70)



(71) R = H, X = H_2
(72) R = glucosyl, X = H_2
(73) R = H, X = O

Colchicine and its derivatives have also been held responsible for some teratological effects,[134] an effect to be related to its anti-mitotic activity. Isolated claims for teratogenesis have been made for heliotrine[135] and for deserpidine,[136] physostigmine,[137] and quinine.[138]

[132] R. F. Keeler, *Phytochemistry*, 1968, **7**, 303; R. F. Keeler and W. Binns, *Teratology*, 1968, **1**, 5.
[133] R. F. Keeler, *Steroids*, 1969, **13**, 579.
[134] M. Guyot, *Compt. rend. Soc. Biol.*, 1963, **157**, 628; N. Foucaunau, R. Stoll, and R. Maraud, *ibid.*, 1963, **157**, 780; B. A. Diwan, *J. Embryol. Exp. Morphol.*, 1966, **16**, 245 (*Chem. Abs.*, 1966, **65**, 19 053); R. Shoji and S. Makino, *Proc. Japan Acad.*, 1966, **42**, 822 (*Chem. Abs.*, 1967, **66**, 36 494*r*); P. Ancel, *Compt. rend.*, 1952, **234**, 2134.
[135] C. R. Green and G. S. Christie, *Brit. J. Exp. Path.*, 1961, **42**, 369.
[136] H. Tuchmann-Duplessis and L. Mercier-Parrot, *Compt. rend. Soc. Biol.*, 1961, **155**, 2291.
[137] I. P. Agarwal, *J. Animal Morphol. and Physiol.*, 1956, **3**, 63 (*Chem. Abs.*, 1958, **52**, 580).
[138] A. P. Belkina, *Arkh. Pathol.*, 1958, **20**, 64 (in Russian) (*Chem. Abs.*, 1959, **53**, 8429).

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