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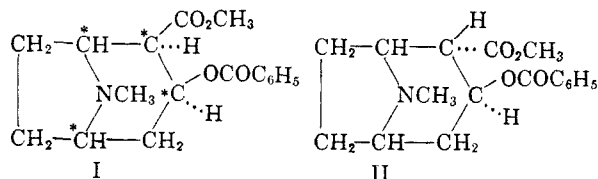
## The Three-Dimensional Structures of the Cocaines. II. Racemic Allococaine and Racemic Allopseudoecocaine

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Catalytic hydrogenation of racemic 2-carbomethoxy-tropinone in acetic acid yields racemic alloecgonine methyl ester, which can be transformed to the racemates of allococaine, allopseudoecgonine, allopseudoecgonine methyl ester, and allopseudoecocaine. Some limitations of a generalization concerning the course of the catalytic hydrogenation of cyclic ketones as it applies to certain keto derivatives of the tropane and morphine alkaloids are noted. The three-dimensional structures of the new cocaines are tentatively assigned. The possible utility of molecular rotation data in ascertaining the absolute configuration of transformation products of the 2-carbomethoxy derivatives of both tropinone and *N*-methylgranatone is indicated. Some other possible methods of synthesizing the new cocaine isomers and the drawbacks thereof are mentioned.

Having established the molecular structure of the naturally occurring and medicinally important alkaloid, *l*-cocaine (I)<sup>1</sup> Willstätter and his collaborators remarked that three other stereoisomers having the same sequence of atomic linkages should exist.<sup>1,2,3</sup> Of these he and his associates obtained, both by the transformation of *l*-cocaine and also by total synthesis, one other stereoisomer, pseudoecocaine (II).<sup>4,5</sup> Although they recorded



the availability of a third,<sup>4</sup> neither of the two remaining cocaine stereoisomers had been isolated when the problem was abandoned some thirty-five years ago.

The isolation of the four possible modifications at that time, while it would have substantiated their predictions based on the fundamental structural theory of organic chemistry, would have left unanswered the related and equally important question as to the steric or three-dimensional relationship of the functional groups in each of them. Although Willstätter had, to be sure, not overlooked this problem, stereochemistry was at that time in too rudimentary a state to permit a certain conclusion; and his opinion concerning the relation of cocaine to pseudoecocaine<sup>2</sup> has indeed recently been disproved.<sup>6</sup>

(1) R. Willstätter and W. Müller, *Ber.*, **31**, 2655 (1898).

(2) R. Willstätter and M. Bommer, *Ann.*, **422**, 15 (1921).

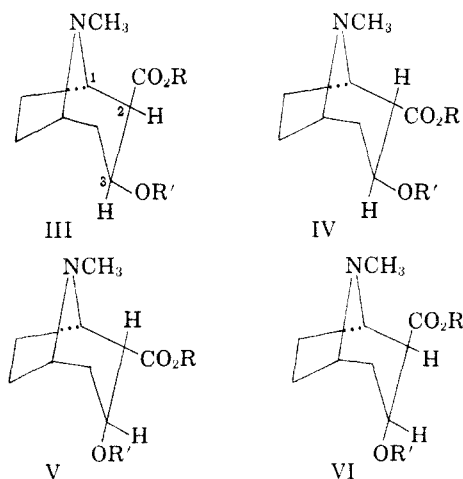
(3) R. Willstätter and A. Bode, *Ann.*, **326**, 42 (1903).

(4) R. Willstätter, O. Wolfes, and R. Mäder, *Ann.*, **434**, 111 (1923); *Cf.*, E. Merck, German Patent 389,359.

(5) *Cf.*, (a) A. Einhorn and A. Marquardt, *Ber.*, **23**, 468 (1890); (b) C. Liebermann and F. Giesel, *Ber.*, **23**, 508 (1890).

(6) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 4624 (1953); **76**, 2855 (1954).

The maturation of stereochemistry which has occurred meanwhile makes possible now the determination of such questions in natural products generally, and, relative to the cocaine problem, has allowed the unequivocal assignment of three-dimensional structures to the known isomers, cocaine and pseudoecocaine (III and IV, respectively, R=CH<sub>3</sub>, R'=COC<sub>6</sub>H<sub>5</sub>).<sup>6-9</sup> By the process of elimination the two unknown isomers must be represented by the structures, V and VI (R=CH<sub>3</sub>, R'=COC<sub>6</sub>H<sub>5</sub> in both); and this information permits a more rational approach to their selective synthesis.



The isolation of these two unknown cocaines would be noteworthy as completing one of the classical topics of alkaloid chemistry. It would also afford ready access to potentially valuable derivatives of the medicinal, atropine; and indeed

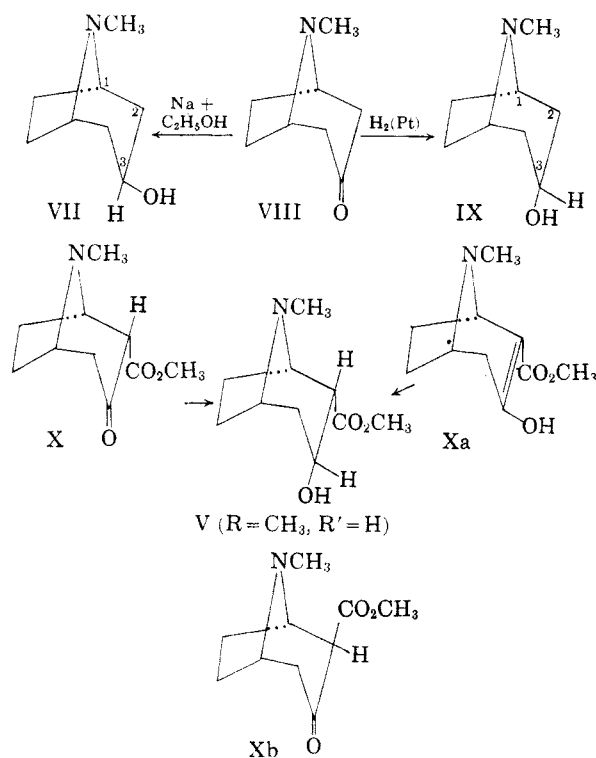
(7) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 1033 (1953).

(8) G. Fodor, *Nature*, **170**, 278 (1952); G. Fodor and Ö. Kovács, *J. Chem. Soc.*, 724 (1953).

(9) According to E. Hardegger and H. Ott these structural formulae rather than their mirror images represent the absolute three-dimensional likeness of the naturally occurring alkaloid and its derivatives [*Helv. Chim. Acta*, **38**, 312 (1955)].

there are recorded few, if any, examples of tropines bearing substituents at the C<sub>2</sub>-position.

The three-dimensional structures of the related substances, pseudotropine (VII) and tropine (IX), have also been established.<sup>10</sup> Reduced with sodium and alcohol, sodium amalgam, or sodium and moist ether, the ketone, tropinone (VIII), affords pseudotropine (VII)<sup>11</sup>; and on catalytic reduction this ketone yields the isomeric amino alcohol, tropine (IX).<sup>12,13</sup> These transformations are, among the tropane alkaloids, remarkably stereospecific, no evidence of the formation of more than one isomer having been found in either the sodium and alcohol<sup>11</sup> or the catalytic reduction of tropinone<sup>12,13</sup> (see experimental section). By the action of sodium amalgam on the 2-carbomethoxy derivative of this ketone, both ecgonine and pseudoecgonine (III and IV, respectively, R = R' = H)<sup>2-4</sup> result in which compounds the C<sub>3</sub>-hydroxyl group thus created has the same steric relation to the nitrogen bridge<sup>6-8</sup> as the similarly produced C<sub>3</sub>-hydroxyl group of pseudotropine.<sup>11</sup> Hence, the catalytic hydrogena-



tion of the keto tautomer (X) of this substance would be an obvious way of attempting the synthesis of the unknown isomers (V and VI); and indeed, as described in more detail hereinafter, this process,

(10) (a) G. Fodor and K. Nádor, *Nature*, **169**, 462 (1952); (b) *J. Chem. Soc.*, 721 (1953); (c) L. F. Fieser and A. Nickon, *J. Am. Chem. Soc.*, **74**, 5566 (1952).

(11) R. Willstätter, *Ber.*, **29**, 936 (1896).

(12) J. van de Kamp and M. Slettinger, *Chem. Abstr.*, **39**, 2080 (1945).

(13) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).

applied to the keto ester, converts it in excellent yield to alloecgonine methyl ester (V, R = CH<sub>3</sub>, R' = H).<sup>9</sup>

Since, unlike tropinone, 2-carbomethoxytropinone exists largely as the enol (Xa)<sup>14</sup> in solutions most favorable to its catalytic hydrogenation, an adequate explanation of the steric outcome of this process must take cognizance of the possibility that an enolic rather than a carbon-oxygen double bond is reduced. The results of the reduction of some basic ketones carried out in connection with this investigation together with information of a similar kind drawn from the chemistry of the morphine alkaloids permits one to account satisfactorily for the product obtained, regardless of the tautomeric form actually reduced.

According to the nomenclature now customary for specifying the location of ring substituents,<sup>15</sup> the C<sub>3</sub>-oxygen is *equatorial* in molecules having the structures, III, IV, and VII, and *axial* in the structures, V, VI, and IX. As a rule, the reduction of ketones by means of such reagents as sodium and alcohol affords predominantly the *equatorial* configuration of the hydroxyl group,<sup>15</sup> and the well nigh exclusive formation of pseudotropine (VII) (see experimental section) and the equally one-sided production of ecgonine and pseudoecgonine<sup>4</sup> by similar methods apparently provides additional corroboration of this generalization.

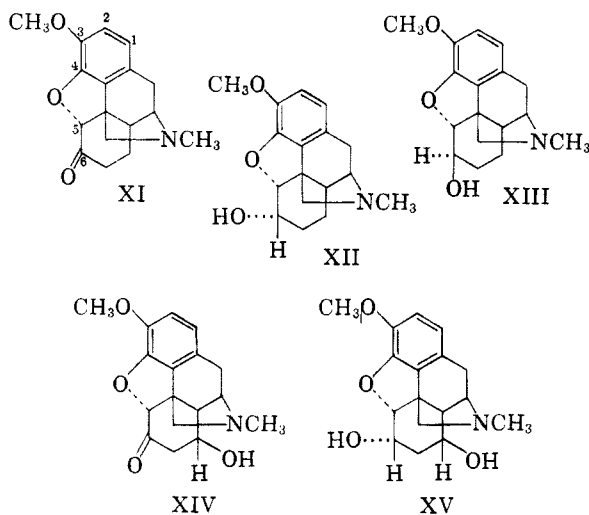
In general the catalytic hydrogenation of both hindered and unhindered cyclic ketones in strongly acidic media is rapid and affords the *axial* configuration of the hydroxyl group formed, while in basic and in neutral media this process is slow and leads to the *axial* configuration only when the ketone is strongly hindered.<sup>15</sup> In this investigation the platinum-catalyzed hydrogenation of tropinone which is not notably hindered was observed to occur at the same rate in alcohol as in aqueous acetic acid, and in both instances the product appeared to consist entirely of tropine (IX) (which has the *axial* configuration of the C<sub>3</sub>-hydroxyl group). It was observed also that in aqueous hydrochloric acid the platinum-catalyzed hydrogenation of dihydrocodeinone (XI) proceeds quite slowly and gives only a mixture of products from which no pure component could be isolated, while in the relatively weakly acidic medium, aqueous acetic acid, this process took place about ten times more rapidly and yields largely dihydrocodeine (XII).<sup>16</sup> Finally, it has been reported that 8-hydroxydihydrocodeinone (XIV) is reduced much more rapidly in alcohol than in aqueous hydrochloric acid and to the same alcohol, presumably

(14) S. P. Findlay, *J. Org. Chem.*, **22**, 1385 (1957).

(15) For an informative discussion of ring conformations and the appertaining nomenclature, consult D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(16) In basic media (pyridine) dihydrocodeinone is also readily hydrogenated to dihydrocodeine. K. Goto and T. Arai, *Ann.*, **547**, 194 (1941).

8-hydroxydihydrocodeine (XV).<sup>17</sup> Quite evidently the foregoing generalization, of undeniable usefulness among most alicyclic compounds, fails in its application to such complex basic ketones as tropinone and dihydrocodeinone; the cause of this failure suggested below has the double advantage of accounting satisfactorily for the catalytic hydrogenation of 2-carbomethoxytropinone, whatever the tautomeric form in which it is reduced, and of indicating the nature of the exceptions to this rule which may be anticipated.<sup>18</sup>



Possibly what may be referred to as *steric accommodation* between the catalyst and the molecule to be reduced (particularly those molecules containing two or more basic atoms), in conjunction with a coordinating power of metallic catalysts for basic atoms like nitrogen and oxygen, outweighs in importance the tendency of a ring to assume a particular conformation and hence to yield a particular configuration of an attached substituent. Many organic compounds, such as certain of the terpenes and sterols, have molecular structures

(17) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **73**, 4001 (1951).

(18) The supposition that catalytic hydrogenation of unsymmetrical cyclic ketones in acidic media (which leads to the alcoholic groups with the *axial* configuration) is rapid<sup>15</sup> appears to be based on the usually lesser thermodynamic stability of an alcohol with an *axial* hydroxyl group relative to the epimeric alcohol in which this group is *equatorial*. Hence, assuming the rate of formation of the latter to be the same in acidic as in basic and in neutral media, the predominant production of the former in acidic media must be due to a marked favouring by acid of the hydrogenation mechanism whereby the former is produced. It is nevertheless conceivable that the *axial* configuration might predominate under such conditions by the reverse process—namely, the inhibition by strong acid of the hydrogenation mechanism whereby the *equatorial* configuration is formed; it has been pointed out that, in at least one or two instances (coprostanone and possibly 2-methylcyclohexanone), the rate of platinum-catalyzed formation of the alcohol having the *axial* configuration of the hydroxyl group in strongly acid media is slower than the rate of formation of the *equatorial* epimer in neutral media (S. P. Findlay, Archives of The Chemical Society, Paper 8/1044).

that are essentially flat and, furthermore, contain no nitrogen which is accessible from only one side of the molecule. In such instances, interaction between either side of the molecule and the catalyst is relatively probable; therefore, ring conformation may be decisive in determining the configuration of the substituent produced by the catalytic hydrogenation. On the other hand, among bridged ring compounds such as the complex morphine alkaloids and the bicyclic terpenes of the camphor type, one side of the molecule is much more convenient to the catalyst than any other—*i.e.*, steric accommodation and/or coordinating power become factors to be considered in the steric course of the hydrogenation of ketones. If these two factors exceed the conformational one in importance, any adherence of such bridged ring compounds to the foregoing generalization arises from the fortuitous circumstance that in the examples so far studied these three influences have usually acted in concert. Only by an examination of instances in which these influences operate in opposing directions can one form some estimate of their relative importance and thus predict intelligently the probable steric course of such hydrogenations generally.

The catalytic hydrogenation of camphor (XVI) and of dihydrocodeinone indicate the possible results of such an examination. In acetic acid the platinum-catalyzed hydrogenation of camphor results in isborneol (XVII)<sup>19,20</sup> in which the hydroxyl group is equatorial.<sup>15</sup> From X-ray crystallographic studies it appears that Ring C of morphine and many of its derivatives may have the boat or semi-boat conformation.<sup>21,22</sup> Hence, the platinum-catalyzed hydrogenation in acidic media of dihydrocodeinone (XI) should, according to the foregoing generalization, convert this ketone largely to dihydroisocodeine (XIII) in which the C<sub>6</sub>-hydroxyl would have the axial configuration for the boat conformation.<sup>22</sup> Such an outcome is, however, contrary to that expected from considerations of coordinating tendencies and of steric accommodation, which generally produce among the morphine alkaloids a C<sub>6</sub>-hydroxyl group *trans* to the nitrogen bridge,<sup>23</sup> as noted above, dihydrocodeine (XII) having presumably an equatorial C<sub>6</sub>-hydroxyl

(19) G. Vavon and P. Peignier, *Compt. rend.*, **181**, 183 (1925).

(20) M. Lipp, E. Oeckinghaus, and C. L. Conze, *Ber.*, **74**, 6 (1941).

(21) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).

(22) K. W. Bentley and H. M. E. Cardwell, *J. Chem. Soc.*, 3252 (1955).

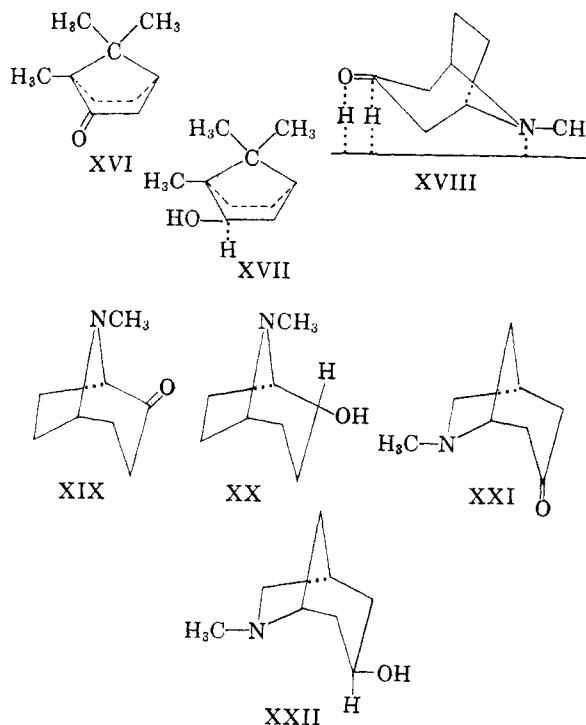
(23) A consideration of the steric factor in the catalytic hydrogenation of morphine C<sub>6</sub>-ketones enabled Fieser to predict correctly the configuration of the C<sub>6</sub>-hydroxyl so produced in this class of compounds. L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Third Ed., Reinhold Publishing Corporation, New York, 1949, pp. 24–25 [Cf., H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1951); *J. Am. Chem. Soc.*, **74**, 2630 (1952)].

group (*trans*, however, to the nitrogen bridge) is in fact produced.<sup>24</sup>

That coordinating power and steric accommodation are highly significant in other, similar types of catalytic hydrogenation makes itself evident from the reduction of the ethylenic and enolic double bonds of the complex alkaloid, thebaine. The numerous products thus obtained<sup>25-27</sup> result from the addition of one, two, or three molecules of hydrogen to the side of the molecule bearing the nitrogen bridge;<sup>28,29</sup> no such products arising from addition to the other side appear ever to have been found.<sup>25</sup>

Among the tropane alkaloids, tropinone constitutes another example wherein these factors may either cooperate or conflict. Because in this instance an acidic medium (which favors the formation of the *axial* configuration) obviously reinforces the effects of coordination and of steric fit, the conversion of tropinone (VIII) in acetic acid to tropine (IX) by catalytic hydrogen is not surprising. That the substitution of alcohol as solvent—which puts the conformational factor in opposition—has no appreciable influence either on the rate of reduction or on the configurational outcome indicates that for this molecule, as for dihydrocodeinone, the steric and coordination factors predominate and hence bring about the addition of hydrogen somewhat as illustrated by the structure, XVIII, regardless of the relative acidity of the solvent. If so, this process applied to the isomeric and isosteric substances, tropanone-2 (XIX and its mirror image) and isotropinone (XXI and its mirror image), may afford substantial quantities of tropanol-2 (XX and its mirror image) and isopseudotropine (XXII and its mirror image), respectively, wherein the newly created hydroxyl groups are equatorial, the relative acidity of the solvent notwithstanding.

Hydrogenated in the keto form, 2-carbomethoxytropinone should, as already noted, resemble tropinone in yielding the tropine configuration of the C<sub>2</sub>-hydroxyl group. If it is hydrogenated in the enol form, the conformational factor is eliminated; steric accommodation and coordination power, operating by analogy with the catalytic reduction of the enolic double bond of thebaine to neopine methyl ether<sup>27</sup> and to tetrahydrothebaine<sup>25,26</sup>



should produce the tropine configuration also. Hence, the conversion of this  $\beta$ -keto ester to alloecgonine methyl ester (V, R=CH<sub>3</sub>, R'=H) appears to harmonize very well with pertinent available information concerning such processes.

The platinum-catalyzed hydrogenation of racemic 2-carbomethoxytropinone (X or Xa and its antipode) in aqueous acetic acid gives the  $\beta$ -hydroxy amino ester, racemic alloecgonine methyl ester (V and its antipode, R=CH<sub>3</sub>, R'=H) in high yield (*ca.* 80%). As described in the experimental section this process was attempted under a variety of conditions. Of particular note are the observations that methanol and benzene are poor or unsatisfactory solvents for the hydrogenation and that hydrogen chloride markedly retards the reduction.<sup>30</sup>

Racemic alloecgonine methyl ester, the only reduction product found, can be readily isolated and purified as its acetate. The free ester, C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>, which melts at 81.5–83.5°, resembles the long known methyl esters of ecgonine and pseudoeccgonine in physical and chemical properties. Sublimation or distillation *in vacuo* except at low temperatures causes a pronounced decrease in its melting point; and, when hydrolyzed, it affords racemic allopseudoeccgonine (VI and its antipode, R=R'=H), C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>, melting at 243°, in about the same quantity as racemic alloecgonine (V and its antipode, R=R'=H), C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>, melting at 241°. The former amino acid gives upon Fischer esterification the expected C<sub>2</sub>-epimer, racemic

(30) Aqueous hydrochloric acid appears to be quite satisfactory as a medium for hydrogenating 3-carbomethoxy-1,2,6-trimethylpiperidone-4. C. Mannich, *Arch. Pharm.*, **272**, 323 (1934).

(24) If, as suggested,<sup>21</sup> the C<sub>6</sub>-hydroxyl group of dihydrocodeine and its near relatives is equatorial, the retarding influence of hydrochloric acid on the catalytic process leading to these substances is explicable.<sup>18</sup>

(25) C. Schöpf and L. Winterhalder, *Ann.*, **452**, 232 (1927).

(26) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

(27) L. F. Small, *J. Org. Chem.*, **20**, 953 (1955).

(28) G. Stork, *The Alkaloids*, R. H. F. Manske and H. L. Holmes, Eds., Vol. II, Academic Press, New York, 1952, pp. 175 and 199.

(29) Cf., K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, Oxford at the Clarendon Press, London, 1954, pp. 197–203.

allopseudoecgonine methyl ester (VI and its antipode, R=CH<sub>3</sub>, R'=H), C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>, which melts at 80°.

Although the melting points of the two new ecgonine methyl esters lie close together, mixtures of the two melt much lower; and their distinctive salts and infrared spectra leave no doubt concerning their non-identity. Likewise, a mixture of racemic alloecgonine and the allopseudo isomer melts much lower than either component, and their hydrochlorides (melting at 231–233° and at 213° respectively) and differing capacity for hydrate formation make their dissimilarity indubitable.

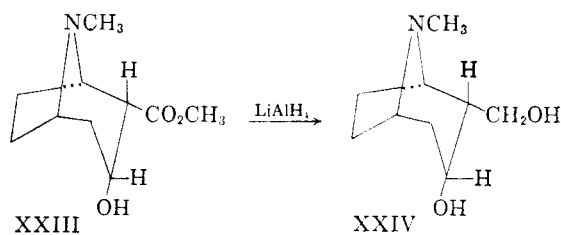
From the large-scale reduction of racemic 2-carbomethoxytropinone with sodium amalgam, Willstätter and his collaborators obtained, besides racemic ecgonine and racemic pseudoecgonine, a small quantity of a third substance, which he called the 'drittes racemisches Ekgonin'.<sup>4</sup> This melted at 229° (corr.) and afforded a hydrochloride melting at 231°. Assuming the reliability of the data noted above, one may reasonably infer that their hydrochloride was pure or nearly pure racemic alloecgonine hydrochloride and that their free 'drittes racemisches Ekgonin', because of the ready epimerization of alloecgonine methyl ester, contained both the allo and allopseudo ecgonines.

The three-dimensional structures assigned above to the allo and allopseudo series derive primarily from the reactivities of the methyl esters toward methyl iodide. The variety of products got from the reaction of ecgonine methyl ester and this alkiodide<sup>4,6</sup> arises from the *trans* relation of the C<sub>2</sub>-hydrogen and the nitrogen atom, Hofmann Degradation being thus possible by the relatively facile *trans* elimination process and further promoted by the electrophilic C<sub>2</sub>-carbomethoxy group.<sup>6</sup> Only the expected methiodide results from the combination of methyl iodide with pseudoecgonine methyl ester<sup>4,6</sup> in which the C<sub>2</sub>-hydrogen is in the *cis*-position relative to the nitrogen atom. Racemic alloecgonine methyl ester yields readily a pure methiodide, C<sub>11</sub>H<sub>20</sub>INO<sub>3</sub>, melting at 196–197°, both from methanol and from acetone, while the allopseudo isomer affords, under the same circumstances, a mixture of products from methanol from which no methiodide was obtained and only a poorly defined methiodide from acetone. One may conclude tentatively that allopseudoecgonine methyl ester and its derivatives have the ecgonine methyl ester configuration of C<sub>2</sub> in which the hydrogen and carbomethoxy groups are attached *trans* and *cis*, respectively, to the nitrogen atom, while the pseudo and the allo series are alike in having the C<sub>2</sub>-hydrogen and -carbomethoxy groups attached *cis* and *trans*, respectively, to the nitrogen atom.<sup>31</sup> The spatial location of the C<sub>3</sub>-hydroxyl having been ascertained above and the configurational relation of the optically active 2-carbomethoxytropinones to *l*-cocaine having been estab-

lished,<sup>14</sup> the three-dimensional structures assigned throughout this discussion follow.

Since the C<sub>3</sub>-hydroxyl groups of the two new ecgonine methyl esters have the *axial* configuration and are otherwise hindered, a greater resistance to benzylation might be anticipated; benzoyl chloride in pyridine, which was the most effective technique employed, did give a low yield (ca. 40%) of racemic allococaine, C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub> (m.p. 82–84°), and hardly more than a trace of racemic allopseudoecocaine, C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub> (m.p. 93–95°). As methyl benzoate was liberated during the benzylation of both esters in noticeable degree, the pyridine-catalyzed decomposition of the new cocaines contributes to the difficulty of realizing a satisfactory yield. This propensity to transesterification is such that the pure bases appear to autocatalyze their decomposition, the odorless crystals of each of the new racemic cocaines gradually changing to a brown oil and emitting the unmistakable aroma of methyl benzoate. The physical and chemical properties of the new racemic cocaines do not depart noticeably from those of the known isomers. Some impression of the similarities and differences between them may be obtained from Table I.

The extensibility of the foregoing procedures to the acquisition of the optically active antipodes of the allo and allopseudo series was established in the ready conversion of *d*- and *l*-(2-carbomethoxytropinone) to the corresponding optically active alloecgonine methyl esters. No evidence of racemization or other unexpected phenomena like that reported by Mannich<sup>30</sup> was noticed. In methanol *d*-alloecgonine methyl ester is weakly dextrorotatory ( $\alpha_D^{20} +0.15 \pm 0.03$ ) and affords a strongly laevorotatory ecgonine ( $\alpha_D^{20}$  ca.  $-47^\circ$  in water). Reduced with lithium aluminum hydride in tetrahydrofuran this ester (XXIII) was converted to a substance, presumably alloecgoninol (XXIV), C<sub>9</sub>-



(31) Evidence of an indirect character supports this conclusion. If 2-carbomethoxytropinone is hydrogenated in the enol form,<sup>14</sup> hydrogen should add, for reasons already given, in a *cis* manner from the side having the nitrogen bridge creating the structure, V (R=CH<sub>3</sub>, R'=H); if in the keto form, of the two possible and interchangeable configurations at C<sub>2</sub> (X and Xb), that (X) in which the carbomethoxy group is *trans* to the nitrogen bridge and, presumably, *equatorial*, appears to be the stabler one, and this would be frozen by the reduction of the keto group.

Also, racemic allopseudoecgonine combines with methanolic methyl iodide, the corresponding methyl ester resulting [Cf., ref. 6; also F. G. Novy, *Am. Chem. J.*, **10**, 145 (1888)].

TABLE I  
MELTING POINTS OF THE RACEMIC COCAINES AND SOME OF THEIR DERIVATIVES

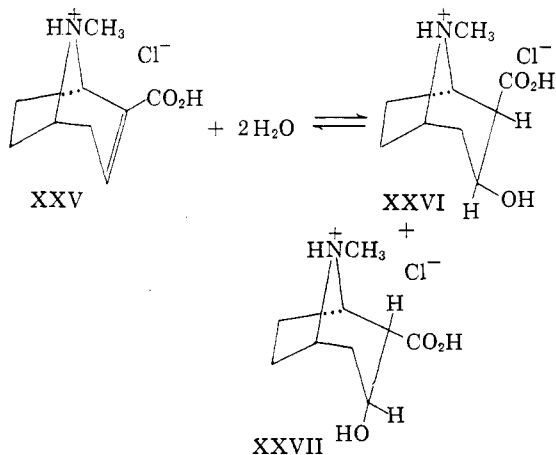
Cocaine Modifications	Racemic Cocaine		Derived Racemic Ecgonine Methyl Ester		Derived Racemic Ecgonine	
Naturally occurring hydrochloride	79–80 <sup>°4</sup>	187 <sup>°4</sup>	Liq. <sup>4</sup>	195 <sup>°4</sup>	212 <sup>°4</sup>	247 <sup>°4</sup>
Pseudo hydrochloride	81.5 <sup>°3</sup>	205.5 <sup>°3</sup>	128 <sup>°3</sup>	—	251 <sup>°3</sup>	193–194 <sup>°3</sup>
Allo hydrochloride	82–84 <sup>°32</sup>	201.5 <sup>°32</sup>	81.5–83.5 <sup>°32</sup>	—	241 <sup>°32</sup>	233 <sup>°32</sup>
Allopseudo hydrochloride	93–95 <sup>°32</sup>	—	80 <sup>°32</sup>	192 <sup>°32</sup>	243 <sup>°32</sup>	213 <sup>°32</sup>

H<sub>17</sub>NO<sub>2</sub>, melting at 201.5–202.8°, which was also optically active ( $\alpha_D^{20} -6.3$ , in water).

The foregoing synthetic scheme is simple and unambiguous; and, were it not for the benzoylating reaction which can no doubt be improved, the overall yields would be high. Moreover, as it leads to both antipodes of each of the new cocaines, it constitutes a complete solution of the problem, while a scheme based on the transformation of *l*-cocaine can afford but one antipode of each. Several approaches to a limited solution of the latter kind were considered, but investigation showed them to be unpromising. For example, the oxidation of the methyl esters of ecgonine and pseudoecgonine to *d*-(2-carbomethoxytropolinone) in substantial quantity proved impracticable;<sup>14</sup> while an S<sub>N</sub>2 displacement reaction involving the tosyl derivatives of these esters might allow the desired inversion of the configuration at C<sub>3</sub>, the preparation of the requisite tosylates is difficult.<sup>33</sup>

(32) See experimental section.

(33) The mutarotation of salts of anhydroecgonine (XXV) in aqueous solution (A. W. K. de Jong, *Rec. trav. chim.*, **42**, 996–7 (1923)), which is no doubt due to hydration of the  $\alpha,\beta$ -ethylenic linkage, suggests another avenue of access. This phenomenon which, among simple aliphatic compounds, has been studied extensively by Lucas and his collaborators [see, e.g., D. Pressman and H. J. Lucas, *J. Am. Chem. Soc.*, **64**, 1953 (1942)] now finds exemplification among the  $\alpha,\beta$ -unsaturated ketones derived from morphine<sup>17</sup> [U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957)]. An equilibrium involving ecgonine (XXVI) and alloecgonine (XXVII) in the salt form is thus quite conceivable:

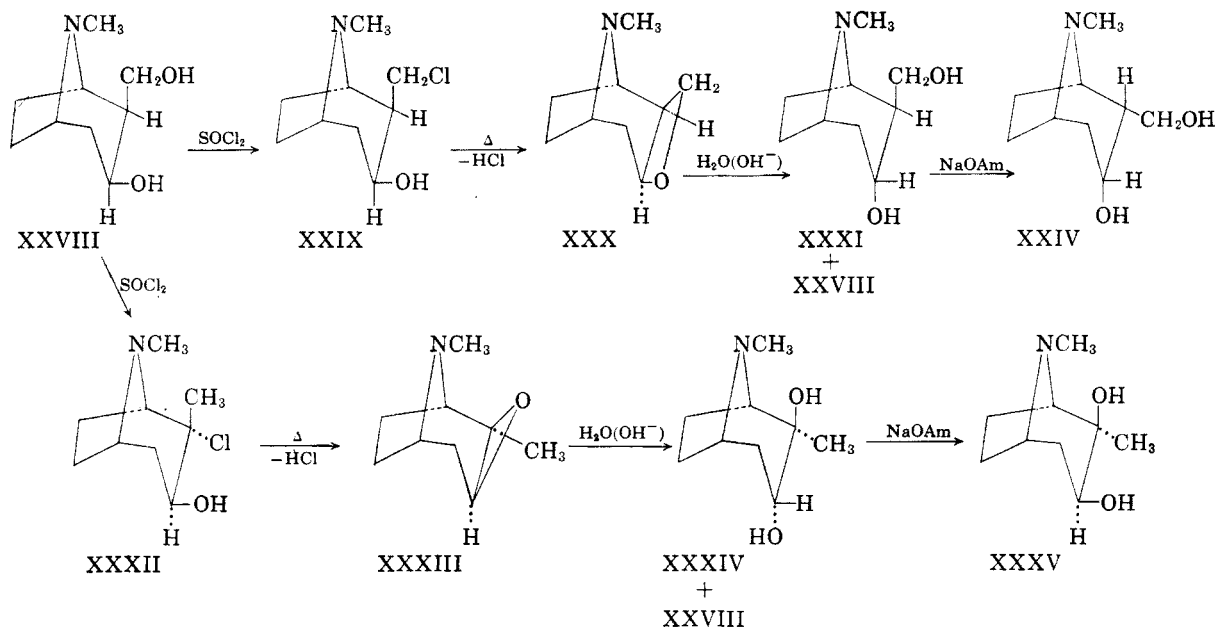


Still another variation of this kind of attack, which has been attempted elsewhere,<sup>34</sup> involves the use of ecgoninol (XXVIII), the lithium aluminum hydride reduction product of cocaine. Thionyl chloride is said to convert this diol to the chlorohydrin (XXIX) which heat transforms to an ether, possibly XXX.<sup>34</sup> By the action of hydroxide the ether reverts in part to ecgoninol (XXVIII) and gives in part a new isomeric diol to which the structure, XXXI, is assigned<sup>34</sup>; this is isomerized with sodium amylate to a product which, if the preceding part of the scheme is correctly represented, should be alloecgoninol (XXIV). However, the reported melting points of this substance and its hydrochloride differ appreciably from those of the alloecgoninol and its hydrochloride described above. In view of the reduction of cocaine to ecgoninol with lithium aluminum hydride in the expected manner,<sup>8</sup> the similar reduction of alloecgonine methyl ester permits no alternative to the structure, XXIV, for the product so obtained in this investigation. It is therefore reasonable to suppose that the foregoing chlorohydrin is a rearrangement product and that an alternative sequence, perhaps XXVIII→XXXII→XXXIII→XXXIV→XXXV, is the correct one. The selective oxidation of alloecgoninol and of allopseudoecgoninol would give optically active alloecgonine and allopseudoecgonine, respectively,<sup>34</sup> which could, of course, be transformed to the hitherto unknown cocaines in the manner indicated above. The successful oxidation in this manner of the two diols obtained by the foregoing reaction sequence has apparently not yet been realized.<sup>35</sup>

Although the rotatory powers of *l*-cocaine and its derivatives have not been measured in a uniform manner, the chemical literature contains enough usable data of this kind to warrant the conclusion,

(34) Ö. Kovács, I. Weisz, P. Zoller, and G. Fodor, *Helv. Chim. Acta*, **39**, 99 (1956).

(35) It has recently been reported also (K. Zeile and W. Schulz, *Chem. Ber.*, **89**, 678 (1956)) that a third racemic cocaine, C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>·½H<sub>2</sub>O, m.p. 156–157°, is obtainable by converting Willstätter's 'drittes racemisches Ekgonin' to the corresponding methyl ester, C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>·½H<sub>2</sub>O, m.p. 203.5°, and benzoylating this. No information concerning the purity of the starting material, the removability of the hydrated water, the properties of appropriate derivatives, or the three-dimensional structure was furnished.



suggested earlier,<sup>14</sup> that the simpler derivatives of the naturally occurring base have a molar rotation more positive (or less negative) than that of the corresponding salts (Table II), and *vice versa* for the derivatives of the unnatural or antipodal base. Among the pseudo derivatives some exceptions to the rule occur, but for asymmetric derivatives of such compounds as 2-carbomethoxytropinone and 2-carbomethoxy-*N*-methylgranatonine the determination of the sign of this difference for several closely related base-salt pairs is sufficient to decide the absolute configuration or three-dimensional structure of the substance in question.

The synthesis of the racemic forms of allococaine and allopseudo cocaine together with the ready accessibility of *d*- and *l*-alloecgonine methyl ester reduce the preparation of the optically active isomers of the allo and allopseudo series as yet unknown to a routine laboratory assignment; together with confirmatory evidence for the three-dimensional structures tentatively proposed herein, this preparation will complete a chapter of classical alkaloid chemistry begun seventy-five years ago.

#### EXPERIMENTAL<sup>37</sup>

**Materials.** The racemic and optically active forms of 2-carbomethoxytropinone employed herein were obtained as described elsewhere.<sup>14</sup> The platinum oxide came from one batch and was a product of the American Platinum Works.

**The catalytic hydrogenation of racemic 2-carbomethoxytropinone.** In a typical experiment anhydrous racemic 2-carbomethoxy tropinone (9.00 g., 0.0456 mole), dissolved in glacial acetic acid (195 ml.) and water (30 ml.), and platinum oxide (0.75 g.) were shaken with hydrogen at 1.3 atmospheres for 48 hr., at the end of which period the con-

sumption [1100 ml. (S.T.P.), 108%] of gas had nearly ceased. The catalyst-free solution was concentrated *in vacuo* on a warm water bath to a viscous, nearly colourless gum which was treated cautiously with water (15 ml.) and saturated aqueous potassium carbonate (50 ml.), the resulting white mixture then being extracted with ether (4 × 100 ml.). Unreduced keto ester was removed by washing with saturated aqueous potassium carbonate (20 ml.) mixed with 3*N* aqueous potassium hydroxide (4 ml.), the potassium salt separating in a yellow solution between the ethereal and the colourless aqueous phases (omission of this step did not noticeably interfere with the isolation of the pure reduction product). Concentration of the dried (sodium sulfate) extracts on a water bath (*ca.* 50°), first at atmospheric pressure and then *in vacuo*, afforded a nearly colourless viscous oil which crystallized when seeded with racemic alloecgonine methyl ester: 8.9 g. (98%). As the ester is always impure at this stage, the oil was as a rule taken up at once in acetone (25 ml.) and ether (50 ml.) and the solution treated with glacial acetic acid (2.55 ml.) in ether (20 ml.). Left for several hours, the yellowish solution deposited white crystalline warts of the *hydroacetate* which were collected: 7.5 g. (64%), m.p. 108–110°. By concentrating the mother liquors *in vacuo* and taking up the residue in a little acetone and ether, a second (*ca.* 1.5 g.) and a small third crop of the salt were also obtained, the total yield of acetate in several such experiments varying between 77 and 83%. Dissolved in water (50 ml.), treated with saturated aqueous potassium carbonate (50 ml.), and processed as above described for the crude ester, the acetate (9.15 g.) yielded colourless *racemic alloecgonine methyl ester* as a thick oil which crystallized spontaneously on keeping: 6.6 g. (94%), m.p. 81.5–83.5°.

Conducted in the foregoing manner, the rate of catalytic hydrogenation of racemic 2-carbomethoxytropinone was in three identical preparations remarkably constant, even at the beginning when it is most rapid. Furthermore, the scale of operations scarcely affects either the rate or the yield. Several variations of this method were also tried with the same hydrogenation apparatus and gas pressure. The use of glacial acetic acid as solvent did not appreciably alter the rate. As expected, the rate was approximately proportional to the relative quantity of catalyst employed. In methanol the rate was about half that in aqueous acetic acid and in benzene it was very low: in these experiments the reduction product was not isolated. In either methanol or glacial acetic acid the hydrogenation of 2-carbomethoxytropinone

(36) C. Lieberman, *Ber.*, 21, 2342 (1888).

(37) The melting points recorded herein are corrected and were observed in boro-silicate glass capillaries. Unless noted otherwise, rotations are for solutions in absolute methanol.

TABLE II  
MOLECULAR ROTATION DIFFERENCES OF BASE-SALT PAIRS AMONG THE COCAINE ALKALOIDS

	Solvent	$[\alpha]_D^{20}$	$[M]_D^{20}$	$\Delta[M]_D^{20}$
l-Cocaine	Methanol	-29.9 <sup>32</sup>	-9,060	+13,400
	Hydrochloride	Methanol	-66.4 <sup>32</sup>	
Ecgonine	Water	-45.5 <sup>36</sup>	-8,420	+2,100
	Hydrochloride	Water	-47.4 <sup>36</sup>	
Pseudoecgonine	Water	+22.7 <sup>6</sup>	+4,200	-400
	Hydrochloride	Water	+21 <sup>5</sup>	
Ecgonine methyl ester	Methanol	-12.3 <sup>6</sup>	-2,450	+9,350
	Hydrochloride	Methanol	-50 <sup>5</sup>	
Pseudoecgonine methyl ester	Water	+22.8 <sup>6</sup>	+4,540	-990
	Hydrochloride	Water	+23.4 <sup>6</sup>	
Anhydroecgonine	Water	-84.6 <sup>33</sup>	-14,100	+800
	Hydrochloride	Water	-73.5 <sup>33</sup>	
d-(2-Carbomethoxytropinone)	Water	+36.7 <sup>14</sup>	+7,230	+5,680
	Ammonium ion	Water	+7.83 <sup>14</sup>	
Pseudoecgoninol	Water	+58.3 <sup>8</sup>	+10,000	+400
	Hydrochloride	Water	+46.3 <sup>8</sup>	
Alloecgoninol	Water	-6.3 <sup>32</sup>	-1,080	+150
	Hydrochloride	Water	-5.9 <sup>32</sup>	
d-Alloecgonine methyl ester	Methanol	+0.15 <sup>32</sup>	+29	+524
	Hydrochloride	Methanol	-2.1 <sup>32</sup>	

hydrochloride was extremely slow. The optically active forms of the keto ester as the bitartrate were readily reduced in aqueous solution, but the yield of alloecgonine methyl ester was much inferior to that obtained when aqueous acetic acid was used. Ruthenium on charcoal, which is advertised as a powerful catalyst for reducing keto groups, had little or no activity in this reaction either in benzene, in methanol or in aqueous acetic acid. Also, rhodium (5% on alumina) had no hydrogenating activity for solutions of the keto ester in methanol.

The catalytic hydrogenation of tropinone in alcohol and in aqueous acetic acid. Tropinone (1.40 g., 0.0100 mole), dissolved in 95% alcohol (37 ml.), was mixed with platinum oxide (0.12 g.) and shaken with hydrogen (at ca. 1.3 atm.). After 6 hr. the uptake of hydrogen had become negligible, the total consumption being then 233 ml. (S.T.P.) (104%). The catalyst-free, colourless solution, which had originally been brownish, was mixed with picric acid (2.30 g., 0.0100 mole) in hot alcohol (30 ml.). Tropine picrate separated at once and was filtered from the cold solution: 3.1 g., m.p. 295°. An additional quantity (0.6 g., m.p. 293°) was isolated from the mother liquors, the total yield of tropine thus being quantitative.

Exact repetition of the foregoing experiment in aqueous acetic acid (32 ml. of glacial acetic acid and 5 ml. of water) gave similar results. The plot of gas consumption as a function of time was colinear with that of the previous preparation for the first 150 minutes, and after 5.5 hr. the total uptake amounted to 105% of the theoretical. Concentrated *in vacuo*, the catalyst-free solution yielded a nearly colourless oil which was mixed with water (10 ml.) and saturated aqueous potassium carbonate (20 ml.). Extraction of the liberated bases with ether (5 × 25 ml.) and removal of the solvent from the dried (Na<sub>2</sub>SO<sub>4</sub>) extracts furnished a colourless liquid which could not be induced to crystallize by seeding either with tropine or with pseudotropine.

The base was heated briefly at 100° with potassium hydroxide (1.0 g.) in water (11 ml.), which caused the formation of a black product also obtainable by similarly treating tropinone. After mixing with some potassium carbonate sesquihydrate, the base was recovered by ether extraction as before: 1.25 g., which crystallized when seeded with tropine. Recrystallized from ligroin it melted at 54–62°. The base was then converted entirely to the picrate as described above: 3.0 g. (81%), m.p. 293–295°.

*Pseudotropine*. Tropinone (10.0 g.) was reduced with sodium and alcohol according to the directions of Willstätter.<sup>11</sup> The reduction mixture was mixed with water (100 ml.), the liberated alcohol removed *in vacuo*, and the residue extracted with ether (6 × 100 ml.). The dried (K<sub>2</sub>CO<sub>3</sub>) extracts furnished a brown oil which readily crystallized with the evolution of considerable heat. This was freed of brown gummy by-products by sublimation *in vacuo*: 9.3 g. (93%). The product was further purified by dissolving the sublimate in benzene (12 ml.) and adding hot ligroin (60–71°) (16 ml.); white prisms, m.p. 106–108°. In three such experiments the yields of pure product were 78, 80, and 82%.

The brown residue from the sublimation which partially crystallizes on keeping gave, upon chromatographing on alumina, as the only crystalline component, a small additional quantity of pseudotropine, m.p. 108–109.5°; methiodide, m.p. 323° (dec.).

The catalytic hydrogenation of dihydrocodeinone. (a) *In hydrochloric acid*. Dihydrocodeinone (3.00 g., 0.0100 mole), m.p. 196–198.5°, dissolved in 3.1N hydrochloric acid (13.2 ml.) and water (16.8 ml.) was shaken with platinum oxide (0.10 g.) and hydrogen ca. at 1.3 atmospheres for 36 hr. (uptake: ca. 170 ml., S.T.P.). The old catalyst was then replaced with fresh and the shaking continued for a like interval. The total uptake of hydrogen by the base was about 350 ml. (S.T.P.) (78% of the theoretical quantity for the consumption of 2 equivalents). The catalyst-free solution contained much free phenolic material as indicated by a strongly positive diazosulfanilic acid reaction. Treated with some sodium hydrosulfite and made basic with potassium bicarbonate, the mixture liberated an oily mixture extractable with chloroform. The recovered oil (3.05 g.) did not crystallize on long keeping; and, when treated with picric acid, gave a liquid picrate which only partially crystallized and could not readily be resolved into its component salts.

(b) *In aqueous acetic acid*. Dihydrocodeinone (3.00 g., 0.0100 mole), m.p. 196–198.5°, dissolved in a mixture of glacial acetic acid (32 ml.) and water (7.0 ml.), was shaken with platinum oxide (0.12 g.) and hydrogen as before. At the beginning the uptake of gas was quite rapid, and after 3 hr. it had nearly ceased: 232 ml. (S.T.P.) (103% of the theory for 1 equivalent). The catalyst-free solution gave a negative diazosulfanilic acid response. Recovered as noted above for tropine in this solvent except that chloroform (3 × 25 ml.) was used, the amber gum did not crystallize on



keeping. Dissolved in ethyl acetate containing a little water, it gave no crystals on scratching, but largely crystallized when seeded with authentic dihydrocodeine hydrate: 2.3 g. (73%).

*Racemic alloecgonine methyl ester hydroacetate.* Prepared as described above, this salt was purified from acetone-ether from which it separated as aggregates of stout prisms, m.p. 110–110.5°. It is extremely soluble in most polar solvents, and even small quantities of acetic acid greatly retard both the inception and the rate of its crystallization.

*Anal.* Calcd. for  $C_{12}H_{21}NO_3$ : C, 55.58; H, 8.16. Found: C, 55.66; H, 8.20.

*Racemic alloecgonine methyl ester.* Isolated from the hydroacetate as described above for the hydrogenation mixture, the oily pure ester crystallized spontaneously and slowly to a white cake. It was recrystallized both from acetone and from ligroin (60–71°) and separated from the former as irregular crystals and parallelepiped and from the latter as striated square tablets, m.p. 81.5–83.5°. It is quite soluble even in the cold in most polar and non-polar solvents. When evaporatively distilled or sublimed *in vacuo* at higher temperatures, the ester appeared to be partially epimerized as indicated by a decline of the melting point to as low as 70–73°.

*Anal.* Calcd. for  $C_{10}H_{17}NO_3$ : C, 60.28; H, 8.60. Found: C, 60.44; H, 8.82.

The pure ester (0.060 g.) in methanol was mixed with picric acid (0.040 g.) in methanol and heated with enough more solvent to complete solution; shiny yellow flakes, m.p. ca. 185°, separated. Recrystallized from methanol, the *picrate* melted at 194–197°, then crystallized partially as the temperature was raised and remelted completely at 203.5°. Recrystallized again, this salt melted at 195–196° (softening at 193°). By lowering the bath temperature to 185° the salt solidified completely and then remelted only at 203–203.5°.

*Anal.* Calcd. for  $C_{16}H_{20}N_4O_{10}$ : N, 13.08; Found: N, 13.11.

The neutral oxalate was prepared in methanol-ether and purified from methanol. It dissolved rather slowly in methanol from which it separated readily only after seeding: warts of feathery, slender prisms, the melting point of which appeared to depend somewhat on the rate of heating but usually occurred about 200.5°.

*Anal.* Calcd. for  $C_{22}H_{36}N_2O_{16}$ : C, 54.08; H, 7.43. Found: C, 53.84, 53.77; H, 7.31, 7.46.

The *hydrochloride* was not obtained crystalline either from methanol or from methanol-ether.

*Racemic alloecgonine.* Hydrolyzed in the same manner as pseudoecgonine methyl ester,<sup>6</sup> racemic alloecgonine methyl ester afforded a white crystalline residue which was contaminated with a purplish impurity when the starting material had not been freed of small amounts of unhydrogenated 2-carbomethoxytryptinone. Leaching the dried hydrolysis product with small amounts of absolute alcohol removed one of its two principal components. The remainder (m.p. ca. 235°) was then evaporated at room temperature with the stoichiometric amount of hydrochloric acid and the recovered salt recrystallized from absolute alcohol from which it is readily purified: colourless crystals of *alloecgonine hydrochloride*, m.p. 231.5–233.5°. The hydrochloride of Willstätter's 'drittes racemisches Ekgonin' is reported to melt at 231°.<sup>4</sup>

*Anal.* Calcd. for  $C_9H_{16}ClNO_3$ : C, 48.76; H, 7.28. Found: C, 49.02; H, 7.18.

The hydrochloride (0.27 g.) in water solution (10 ml.) was shaken with silver carbonate (0.4 g.), the mixture filtered, excess silver removed with hydrogen sulfide, and the  $Ag_2S$ -free solution evaporated to dryness *in vacuo*. The residue dissolved readily in hot absolute alcohol and the solution suddenly deposited a fine crystalline precipitate: m.p. 239°. This material, presumably the anhydrous modification, is much less soluble in hot absolute alcohol, requires about 300 times its own weight of this solvent for complete solution and, until dissolved, imparts a noticeable

opalescence to the hot mixture. Concentration of such a solution to incipient turbidity and cooling afforded racemic alloecgonine as a finely divided precipitate melting at 237° (dec.). After recrystallization from 95% alcohol it melted at 241.5° (dec.); it separated from alcohol (ca. 90%) as lustrous, thin plates, melting at 240–241° (dec.).

*Anal.* Calcd. for  $C_9H_{16}NO_3 \cdot 1H_2O$ : C, 53.18; H, 8.43. Found: C, 52.90; H, 8.24.

Drying 5 hr. at 100° *in vacuo* removed about half the water of crystallization, and drying 9.5 hr. at 117° *in vacuo* removed all of it. Recovered from aqueous solution it did not melt below 125° and thus appeared to be different from Willstätter's 'drittes racemisches Ekgonin' which, as the hydrate, was reported to melt at 110°, and in the anhydrous condition at 229° (cor.).<sup>4</sup>

*Anal.* Calcd. for  $C_9H_{16}NO_3$ : C, 58.35; H, 7.75. Found: C, 58.17; H, 8.02.

*Racemic Allopseudoecgonine.* From the hot absolute alcoholic leaching of racemic alloecgonine (described above), needles melting at 241° separated as the solution cooled. These were recrystallized to constant melting point from absolute alcohol for analysis: feathery needles, m.p. 243° (dec.).

*Anal.* Calcd. for  $C_9H_{16}NO_3$ : C, 58.35; H, 7.75. Found: C, 58.14; H, 7.95.

This isomer appeared not to crystallize with water. The hydrochloride, obtained by evaporating a solution of the amino acid in the equivalent amount of hydrochloric acid, was purified readily from absolute alcohol: m.p. 213°.

*Anal.* Calcd. for  $C_9H_{16}ClNO_3$ : C, 48.76; H, 7.28; Cl, 16.00. Found: C, 48.64; H, 7.33; Cl, 15.86.

*Racemic allopseudoecgonine methyl ester.* Allopseudoecgonine hydrochloride (1.45 g.) was dissolved in absolute methanol (75 ml.) containing dry hydrogen chloride (6.2 g.); the mixture, protected from moisture, refluxed 4 hr. The solvent was removed *in vacuo*, the residue treated with saturated aqueous potassium carbonate (20 ml.) and water (10 ml.), and the resulting mixture extracted with ether (3 × 100 ml.). Recovered from the dried ( $N_2SO_4$ ) extracts in the same manner as the epimeric ester, the colourless oil obtained crystallized almost at once: 0.9 g. After one recrystallization from ligroin (60–71°) these crystals (0.85 g.) melted at 79–80° and after a second at 80–80.5°. This material consisting of small, colourless, short prisms was sublimed about 60°/1 mm. for analysis. The melting point of its mixture with the racemic *allo* isomer was 60–70°.

*Anal.* Calcd. for  $C_{10}H_{17}NO_3$ : C, 60.28; H, 8.60; N, 7.03. Found: C, 60.03; H, 8.61; N, 7.05.

The ester (0.100 g.) and oxalic acid dihydrate (0.0317 g.) were dissolved in methanol ( $\approx 0.2$  ml.). No crystals were obtained either by keeping the solution or after mixing it with an equal additional quantity of oxalic acid.

The ester (0.10 g.) and picric acid (0.12 g.) were mixed in acetone. No crystals separated. Removal of the solvent left a gum which gradually solidified. Recrystallized from acetone to constant melting point (2×), the *picrate* was obtained as yellow, feathery tufts of minute, slender prisms melting at 135–136.3°.

*Anal.* Calcd. for  $C_{18}H_{20}N_4O_{10}$ : C, 44.86; H, 4.71; N, 13.08. Found: C, 44.80; H, 4.72; N, 12.57, 12.74.

As a by-product of the action of benzoyl chloride on the ester in pyridine, *allopseudoecgonine methyl ester hydrochloride* was obtained as a salt insoluble in pyridine. This was recrystallized to constant melting point (2×) by dissolving in methanol and adding ether: irregular, stout prisms m.p. 191.5–192°.

*Anal.* Calcd. for  $C_{10}H_{18}ClNO_3$ : C, 50.95; H, 7.70. Found: C, 50.60, 50.76; H, 7.57, 7.53.

*Racemic allococaine.* To a stirred mixture of racemic alloecgonine methyl ester (4.0 g., 0.0200 mole) in dry pyridine (10 ml.) at 0° was added benzoyl chloride (1.0 ml.). The mixture which reddened at once was kept 15 minutes at 0° and then mixed with more chloride (1.5 ml.). Originally transparent orange red, the benzoylation mixture gradually

acquired a brownish red opacity. After 12 hr. at room temperature, the mixture contained a few crystals and after two days had become semi-solid. The mixture, which smelled strongly of methyl benzoate, was rubbed with methanol-ether (10 ml. of each) and the solid material was collected at the pump and recrystallized from methanol to constant melting point: 1.2 g., m.p. 201.5° of *allococaine hydrochloride*, consisting of aggregates of minute prisms.

*Anal.* Calcd. for  $C_{17}H_{21}NO_4 \cdot HCl$ : C, 60.08; H, 6.53; Cl, 10.43. Found: C, 59.88; H, 6.57; Cl, 10.37.

The mother liquors from the purification of the hydrochloride furnished additional alkaloid through basification, extraction, and conversion to the neutral oxalate described below: 1.1 g.

The pyridine mother liquors were concentrated *in vacuo*, treated with water and potassium carbonate, and extracted with ether which removed both allococaine and unreacted alloecgonine methyl ester. These were separable by taking advantage of the much greater solubility of the latter in weakly alkaline aqueous solutions: ca. 0.6 g. of each ester. The total yield of the cocaine isolated as the hydrochloride and the binoxalate was about 40%.

The feasibility of benzylation by the Schotten-Baumann method, by Willstätter's method utilizing benzoic anhydride in benzene<sup>4</sup>, by the action of benzoyl chloride in inert neutral solvents, by benzoyl chloride alone, and by transesterification with methyl benzoate was examined. None of these methods appears to give results as satisfactory as benzoyl chloride in pyridine.

Recovered from the pure hydrochloride or the pure binoxalate by basification and ether extraction in the usual manner, *racemic allococaine* was obtained as an initially brownish oil which readily crystallized. It could conveniently be recrystallized from ligroin from which it separated as striated, square tablets melting at 82–84°. During several weeks this alkaloid gradually melts to a viscous brown oil with a liberation of methyl benzoate.

*Anal.* Calcd. for  $C_{17}H_{21}NO_4$ : C, 67.31; H, 6.98. Found: C, 67.30; H, 6.85.

Prepared in and purified from methanol, the *binoxalate* was obtained as long, slender prisms melting at 177.5–178.5°.

*Anal.* Calcd. for  $C_{17}H_{21}NO_4 \cdot H_2C_2O_4$ : C, 58.01; H, 5.89. Found: C, 57.88; H, 5.67.

Its *picrate* was prepared in and purified from methanol: stellate clusters of short, slender prisms, m.p. 178.5–180°.

*Anal.* Calcd. for  $C_{23}H_{24}N_4O_{11}$ : C, 51.88; H, 4.54. For  $C_{23}H_{24}N_4O_{11} \cdot \frac{1}{2}CH_3OH$ : C, 51.46; H, 4.78. Found: C, 51.42, 51.38; H, 4.41, 4.49.

Prepared in methanol (0.35 ml.) from the base (0.30 g.) and L-tartaric acid, the L-bitartrate separated as dense warts, m.p. 144–148°. Recrystallized from methanol, the crystals obtained melted at 145.5–148°. The degree of resolution was not investigated.

*Anal.* Calcd. for  $C_{21}H_{27}NO_{10}$ : C, 55.62; H, 6.00. Found: C, 55.16, 55.22; H, 6.09, 6.13.

The dibenzoyl-L-bitartrate was obtained by mixing the base (0.30 g.) with the acid monohydrate (0.37 g.) in methanol. The salt which precipitated was recrystallized three times from methanol, the melting point being raised successively: 161° to 166° to 168–168.5°. The degree of resolution thus effected was not determined.

*Anal.* Calcd. for  $C_{35}H_{35}NO_{12}$ : C, 63.53; H, 5.33. Found: C, 63.68; H, 5.34.

*Racemic Allopseudococaine.* Racemic allopseudococaine methyl ester (0.50 g.) was treated at 0° with a solution (1.4 ml.) made by diluting benzoyl chloride (2.0 ml.) to 10.0 ml. with pyridine. This mixture was stirred at 0° for 30 minutes and kept overnight at room temperature. Removal of the solvent *in vacuo* left a reddish semi-solid (having an odor reminiscent of methyl benzoate), which was mixed with methanol-ether and a crystalline precipitate, *allopseudococaine methyl ester hydrochloride* (see above), filtered off. The filtrate was concentrated *in vacuo*, the residue

mixed with aqueous sodium bicarbonate, and the liberated oily bases extracted with ether. From the dried ether extracts was recovered a small quantity of greenish brown oil which was induced to crystallize by scratching at dry ice temperature. By several recrystallizations from ligroin (60–71°) and manual separation of the crystals from gummy impurities, pure racemic allopseudococaine was obtained: colorless, irregularly shaped crystals melting at 92.5–98.4° and, after grinding, at 93–95°. Like the allo isomer, these crystals liquefy slowly on standing and acquire the aroma of methyl benzoate.

*Anal.* Calcd. for  $C_{17}H_{21}NO_4$ : C, 67.31; H, 6.98. Found: C, 67.45; H, 6.70.

The *picrate* was prepared in and purified from methanol: m.p. 161–162°.

*Anal.* Calcd. for  $C_{23}H_{24}N_4O_{11}$ : C, 51.88; H, 4.54. Found: C, 51.61; H, 4.10.

A comparison of the reactivities of *alloecgonine methyl ester* and *allopseudococaine methyl ester toward methyl iodide*. Methyl iodide (15 ml.) was diluted to 100 ml. with absolute methanol and racemic alloecgonine methyl ester (0.20 g.), m.p. 81–83°, dissolved in some of this solution (0.50 ml.). Kept at 0° overnight the mixture deposited a compact mass of crystals, and an additional quantity was obtained by adding ether to the mother liquor: m.p. 198°. Recrystallized from methanol the first crop of *alloecgonine methyl ester methiodide* gave colorless crystals melting at 196–197°.

*Anal.* Calcd. for  $C_{11}H_{20}INO_3$ : C, 38.72; H, 5.91; I, 37.2. Found: C, 38.88; H, 5.69; I, 37.0.

Treated in exactly the same way allopseudococaine methyl ester, m.p. 80°, gave no crystalline precipitate even after 44 hr. By diluting with ether to near turbidity and scratching, crystals were obtained: m.p. 175–177°. After one recrystallization from methanol these melted at 208–209°; after two, at 212°. The analysis of this material indicated that it was still impure (*Anal.* Found: C, 40.36; H, 6.14; I, 41.7).

Dissolved in acetone (1.0 ml.) and treated with methyl iodide (0.20 ml.) at 0°, alloecgonine methyl ester (0.185 g.), m.p. 81–83°, gave almost immediately a crystalline precipitate melting at 198° and at 196–197° after mixing with the preparation obtained from methanol.

When allopseudococaine methyl ester (0.20 g.), m.p. 80°, dissolved in acetone (1.0 ml.) was mixed at 0° with methyl iodide (0.20 ml.) and the solution allowed to warm, crystals soon precipitated. Two different samples from this preparation melted at 160–165° and 164–167°. After one recrystallization from methanol the product melted at 166–167°; after two, at 164–165°. Although apparently inhomogeneous, it has the composition of *allopseudococaine methyl ester methiodide*.

*Anal.* Calcd. for  $C_{11}H_{20}INO_3$ : C, 38.72; H, 5.91; I, 37.2. Found: C, 38.33; H, 5.77; I, 37.26.

The reaction of *allopseudococaine with methyl iodide*. Allopseudococaine (0.20 g.), m.p. 243°, was dissolved in hot methanol (10 ml.), the solution cooled somewhat, and methyl iodide (Mallinckrodt A.R., 2.5, ml.) added. The mixture was refluxed for 3 hr. and the volatile solvents removed *in vacuo*. The residual gum gradually crystallized 0.22 g., m.p. 165.5–170°. The crystals, which are extremely soluble in methanol, were recrystallized by dissolving them in a small amount of this solvent and keeping the solution at 0°: colourless crystals, m.p. 182.5–185° (*Anal.* Found: C, 40.83; H, 5.83). This may largely be the methyl betaine hydriodide which like the pseudo isomer<sup>6</sup> seemingly loses hydrogen iodide readily.

The mother liquors from the crystallization were concentrated *in vacuo* to a gum which was taken up in aqueous potassium carbonate and the resulting solution extracted with ether. The oily base (0.030 g.), recovered in the usual manner from the extracts, did not crystallize when seeded with racemic alloecgonine methyl ester (m.p. 81–83°), but did so immediately when treated with a trace of racemic allopseudococaine methyl ester.

*d-Alloecgonine methyl ester.* Hydrogenated in a manner essentially the same as for the racemic modification, *d*-(2-carbomethoxytropinone) yielded the *d*-antipode of *alloecgonine methyl ester*.<sup>14</sup> Hydrogenated in aqueous acetic acid as the bitartrate salt,<sup>14</sup> the  $\beta$ -keto ester gave a yield (67%) of pure acetate lower than was obtained from the racemic  $\beta$ -keto ester, and this salt in water alone gave a lower yield still. The remainder of the hydrogenation product appeared to be non-crystalline. Recovered from the pure hydroacetate as indicated above for the racemic isomer, the *d*-ester was recrystallized from ligroin (60–71°): stout, colourless prisms, m.p. 79–82.3°,  $[\alpha]_D^{20} +0.15^\circ \pm 0.03$  (C, 2).

Prepared from the stoichiometric amount of methanolic hydrogen chloride and recrystallized from methanol-ether the *hydrochloride* was isolated as colourless, hygroscopic, hexagonal, and irregularly formed stout prisms:  $\alpha_D^{20} -2.1^\circ$  (C, 2).<sup>38</sup>

*Anal.* Calcd. for  $C_{10}H_{18}ClNO_2$ : C, 50.95; H, 7.70. Found: C, 51.30; H, 7.80.

Prepared in methanol and purified from methanol-ether and from methanol acetone, the *binoxalate*, as small stout prisms, melted at 164–165°. It was dried *in vacuo* at room temperature for analysis.

*Anal.* Calcd. for  $C_{12}H_{19}NO_7$ : C, 49.82; H, 6.62. Found: C, 49.87; H, 6.63.

The picrate was prepared in and recrystallized from methanol: m.p. 199–201°.

*Anal.* Calcd. for  $C_{15}H_{20}N_4O_{10}$ : C, 44.86; H, 4.71. Found: C, 44.81; H, 4.58.

*l-Alloecgonine methyl ester.* Likewise prepared from *l*-(1-carbomethoxytropinone), the *l*-antipode crystallized from ligroin (60–71°) as stout rectangular prisms, m.p. 78–81°, which *in vacuo* at low temperature gave a sublimate of stout prisms melting at 79.5–81.8°,  $\alpha_D^{20} -0.11^\circ \pm 0.03$  (C, 2).

*Anal.* Calcd. for  $C_{10}H_{17}NO_2$ : C, 60.28; H, 8.60. Found: C, 60.18; H, 8.67.

*Hydrolysis of d-alloecgonine methyl ester.* The ester (5.0 g.) dissolved in water (15 ml.) was heated at 70° until the pH of the solution had been reduced to 8. Evaporation of the solution at low temperature afforded a colourless syrup which when kept *in vacuo* over potassium hydroxide largely crystallized. Taken up in hot absolute alcohol (10 ml.) the syrup gave colourless stout prisms which separated during several hours: m.p. 214–216°. Repeated recrystallization from absolute alcohol furnished a pure or nearly pure substance isomeric with *l*-ecgonine: m.p. 221.5–222° (dec.),  $\alpha_D^{20} -47.4^\circ$  (C, 2, water).<sup>38</sup>

*Anal.* Calcd. for  $C_9H_{15}NO_2$ : C, 58.35; H, 7.75. Found: C, 58.48; H, 8.13.

*Lithium aluminum hydride reduction of d-alloecgonine methyl ester.* Lithium aluminum hydride (ca. 50 mg. altogether) was added in small portions to purified tetrahydrofuran (15 ml.) until effervescence ceased and then a further quantity (0.60 g.). To the gently refluxing solution of the reducing agent another of *d*-alloecgonine methyl ester (1.0 g.) in tetrahydrofuran (10 ml.) was admitted dropwise. After

boiling the mixture 1 hr., the excess reducing agent was decomposed with methyl acetate. The mixture was successively treated with 3*N* aqueous sulfuric acid, tartaric acid (2.0 g.), and potassium carbonate, and the whole continuously was extracted with chloroform for 3 days. Removal of the chloroform gave a light brown oil (0.3 g.) which was readily purified from methanol: colourless, triangularly shaped crystals, m.p. 201.5–202.8°,  $\alpha_D^{20} -6.3^\circ$  (C, 1, water).

*Anal.* Calcd. for  $C_9H_{17}NO_2$ : C, 63.12; H, 10.01. Found: C, 63.45; H, 10.09.

Treated with the stoichiometric amount of methanolic hydrogen chloride the base was converted to the hydrochloride, which was recrystallized from methanol-ether: minute, stout prisms, m.p. 236.5–238°,  $\alpha_D^{20} -5.9^\circ$  (C, 1, water).<sup>38</sup>

*Anal.* Calcd. for  $C_9H_{18}ClNO_2$ : C, 52.04; H, 8.73. Found: C, 51.78; H, 8.86.

The foregoing is presumably what has been called 2 $\alpha$ -hydroxymethyl-3 $\alpha$ -tropanol for which the melting point and that of its hydrochloride are reported to be 165–166° and 172°, respectively.<sup>34</sup> An isomeric substance, said to be 2 $\beta$ -hydroxymethyl-3 $\alpha$ -tropanol (XXXI), has been reported to melt at 139–140° and its hydrochloride at 258–260°.<sup>34</sup>

*Infrared measurements.* All measurements were made with a Perkin-Elmer Model 21 double beam spectrometer with sodium chloride optics. In carbon tetrachloride solution the methyl ester of ecgonine, of pseudoecgonine, of racemic alloecgonine, and of racemic allopseudoecgonine each had unmistakable bands in the regions both of hydroxyl group absorption and of carbomethoxy group absorption. For the foregoing esters, respectively, these had the following locations: 2.83 $\mu$  and 5.79 $\mu$ , 2.79 $\mu$  and 5.80 $\mu$ , 2.83 $\mu$  and 5.81 $\mu$ , and 2.76 $\mu$  and 5.75 $\mu$ .

*Miscellaneous rotations.* An apparently pure sample of cocaine [ $\alpha_D^{20} -15.9$  (C, 4, chloroform),<sup>38</sup> [reported  $-15.9$  (C, 4, chloroform)<sup>39</sup>] was found to have in methanol  $\alpha_D^{20} -29.9^\circ$  (C, 1)<sup>37</sup> and  $-31.0^\circ$  (C, 2).<sup>38</sup> Mallinekrodt cocaine hydrochloride in methanol was found to have  $\alpha_D^{20} -66.4^\circ$  (C, 1)<sup>38</sup> and  $-65.6^\circ$  (C, 2).<sup>38</sup>

Ecgonine methyl ester which had originally  $n_D^{19} 1.4886^6$  and  $\alpha_D^{20} -12.3^\circ$  (C, 2)<sup>6</sup> had, after keeping in the dark in a desiccator over  $CaCl_2$  in excess of four years, acquired a brownish colouration. This was removed by evaporative distillation at 95°/1 mm. The distillate appeared to be pure:  $n_D^{20} 1.4887$ ,  $\alpha_D^{20} -12.75^\circ$  (C, 5, methanol).

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(38) Rotation determined by Mrs. Evelyn G. Peake of this Institute.

(39) I. Heilbron, *Dictionary of Organic Compounds*, Rev. Ed., Vol. I, Eyre and Spottiswood, London, 1953, p. 594.