JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

(Registered in U. S. Patent Office) (Copyright, 1954, by the American Chemical Society)

VOLUME 76 JUNE 14, 1954 NUMBER 11

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

The Three-dimensional Structure of the Cocaines. Part I. Cocaine and Pseudococaine

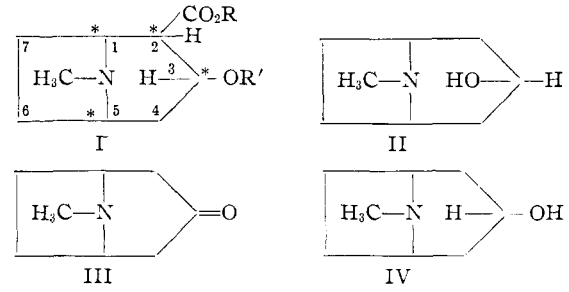
BY STEPHEN P. FINDLAY

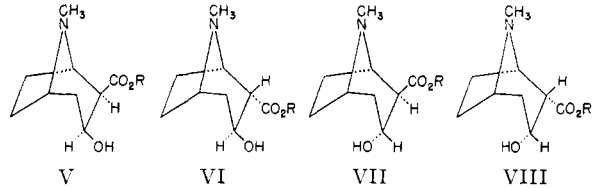
RECEIVED DECEMBER 11, 1953

Published experimental data on the chemistry of cocaine and its simpler derivatives are interpreted as indicating that this base is 2β-carbomethoxy-3β-benzoxytropane and pseudococaine 2α-carbomethoxy-3β-benzoxytropane. Pertinent data in the literature have been verified or corrected. Cocaine is readily transformed by sodium methoxide in methanol to pseudoecgonine methyl ester. Willstätter's ecgonine methylbetaine is in fact the pseudo isomer. O-Benzoylnorecgonine is convertible in the presence of base to the previously unknown N-benzoyl isomer. Names and structures for the other two possible cocaines are proposed.

The numerous contributions, principally by Willstätter and his collaborators, to the chemistry of cocaine were designed to establish its two-dimensional structure. This object was achieved about thirty years ago when cocaine was synthesized from 2-carbomethoxytropinone,[1] and a long chapter of cocaine chemistry was thus concluded. A considerable amount of experimental data incidental to the main purpose of these investigations was necessarily accumulated, and the application of recently developed stereochemical principles to some of this information permits the deduction of the three-dimensional aspect of cocaine and pseudococaine.

It was observed by Einhorn and Marquardt that the hydroxyamino acid, ecgonine (I, R = R′ = H), which is obtained by hydrolyzing cocaine (I, R = CH_3, R′ = COC_6H_5), was converted in hot aqueous potassium hydroxide to a diastereoisomer which, because of its dextrorotation, they called *d*-ecgonine.[2] Later Willstätter demonstrated that tropine (II) and pseudotropine (IV)[3] were epimeric amino alcohols by oxidizing both to tropinone (III)[4] and by isomerizing tropine to pseudotropine with sodium amylate in boiling amyl alcohol.[5] He considered the conditions under which the two isomerizations occurred to be sufficiently similar to warrant the conclusion that the isomerization of ecgonine was an analogous process, *i.e.*, that ecgonine and *d*-ecgonine were epimeric with respect to the secondary hydroxyl group, and he proposed that the latter compound be accordingly named *d*-pseudoecgonine.[1,6] Four diastereoisomers and their enantiomorphs are possible for the sequence of atomic linkages which Willstätter and his collaborators showed was present in cocaine (I, R = CH_3, R′ = COC_6H_5) and in ecgonine (I, R = R′ = H).[7] These are represented three-dimensionally by structures V to VIII. Thus, if ecgonine has struc-





(1) R. Willstätter, O. Wolfes and R. Mäder, *Ann.*, **434**, 111 (1923).

(2) A. Einhorn and A. Marquardt, *Ber.*, **23**, 468 (1890).

(3) The steric relation of the nitrogen atom to the hydroxyl group of tropine and pseudotropine has been proved recently. G. Fodor and K. Nador, *Nature*, **170**, 278 (1952). For additional references, consult E. Hardegger and H. Ott, *Helv. Chim. Acta*, **36**, 1186 (1953).

(4) R. Willstätter, *Ber.*, **29**, 393 (1896).

(5) R. Willstätter, *ibid.*, **29**, 936 (1896).

(6) (a) R. Willstätter and A. Bode, *Ann.*, **326**, 42 (1903); (b) R. Willstätter and M. Bommer, *ibid.*, **422**, 15 (1921); (c) this substance will be hereinafter referred to as pseudoecgonine.

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

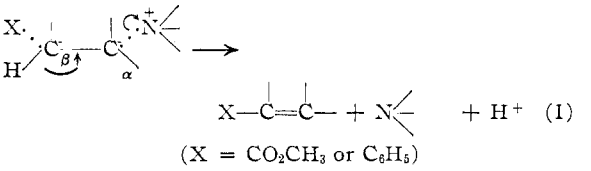
ture V (R = H), pseduoecgonine should, according to Willstätter, be represented by VII (R = H).

It is known, however, from studies of the racemization of optically active acids and esters that the α-hydrogen of carboxylate ions of the type *CHRR'CO_2^-, is labile in alkaline solution and that the α-hydrogen of esters of this type, because of the absence of the negative charge, is relatively more so.[8] Ecgonine is obviously an acid of this type, and the conditions under which it was converted to the pseudo isomer are much more like those under which the foregoing types were racemized than those under which tropine was isomerized to pseudotropine. In this connection it should be noted that, whereas pseudoecgonine is obtained from ecgonine in only 2% yield by exposure to approximately 10% aqueous alcoholic potassium hydroxide for six days, it is obtained in 39 and 54% yields from ecgonine methyl ester and cocaine, respectively, under the same conditions.[9]

It is noteworthy also that ecgonine methyl ester reacts with methyl iodide to furnish a methiodide identical with that from pseudoecgonine methyl ester and methyl iodide.[1] Here too, epimerization at the α-carbon atom, facilitated by the positive charge, has an analogy[8] and accounts well for the rearrangement.[10] For these reasons it appears that Willstätter's opinion was incorrect and that, if ecgonine be V, pseudoecgonine is VI rather than VII.

Dehydration experiments indicate the relation of the hydroxyl and carboxyl groups of ecgonine and pseudoecgonine. The former is largely converted to anhydroecgonine by boiling two hours with phosphorus oxychloride,[11] whereas the latter requires for dehydration four hours exposure at 140° to acetic acid saturated with hydrogen chloride.[2] Also, de Jong found that ecgonine is converted to anhydroecgonine in 80% yield by boiling 12 hours with concentrated hydrochloric acid, whereas, remarkably, the pseudo isomer is little affected by this treatment.[9] Acid-catalyzed dehydration takes place more easily by *trans* elimination than by *cis*,[12] and it may be inferred, therefore, that the carboxyl and hydroxyl groups are *cis* in ecgonine and *trans* in pseudoecgonine.

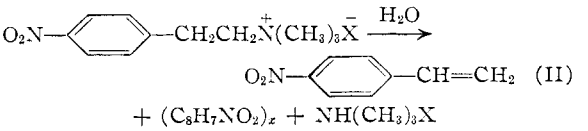
The relation of the carboxyl group and the nitrogen atom of ecgonine can be deduced by the application of stereochemical principles, now well established, to the chemical properties of ecgonine methyl ester and its pseudo isomer reported by Willstätter and his associates. First, they observed that ecgonine methyl ester methiodide underwent Hofmann degradation rapidly in hot, dilute aqueous alkali to give one of the isomeric cycloheptatriene carboxylic acids and dimethylamine, whereas the pseudo isomer decomposed very slowly.[6b] The first step of this decomposition is analogous to that of β-phenylethyltrimethylammonium hydroxide[13] which has been denoted a bimolecular elimination (E-2) reaction,[14] and both may be represented according to the English convention by the partial expression



(X = CO_2CH_3 or C_6H_5)

In such bimolecular processes the principal stereochemical requirement is that the electrons surrendered by the β-hydrogen to the incipient double bond enter the octet of C_α oppositely to the departing nitrogen atom in order that the energy of the transition state be kept as small as possible. When the movements of the participants in this kind of decomposition are restricted, as by inclusion in a ring structure, it may be difficult or impossible to satisfy this steric requirement.[14] Of the pairs of structures, V and VI, VII and VIII (R = CH_3 in all), it is obvious that the former of each has the more favorable (*trans*) disposition of nitrogen and hydrogen for Hofmann elimination.[15]

Secondly, they found that, in the preparation of ecgonine methyl ester methiodide in methanol from its components, some hydriodide salt was obtained as a by-product. Presumably a Hofmann elimination like that undergone by β-*p*-nitrophenylethyltrimethylammonium bromide and iodide had occurred



+ $(C_8H_7NO_2)_x$ + $NH(CH_3)_3X$

Reaction II, carried out in aqueous solution, has first-order kinetics but is markedly accelerated by

(8) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 243–244.

(9) A. W. K. de Jong, *Rec. trav. chim.*, **156**, 186 (1937).

(10) The action of alkali on ecgonine ethyl ester methiodide suggests still another example of epimerization of the α-carbon atom. The product of the reaction was called ecgonine methylbetaine [R. Willstätter, *Ber.*, **32**, 1635 (1899)]. The properties of this methylbetaine do not, however, agree with those of Hesse's ecgonine methylbetaine obtained directly from ecgonine and methyl iodide [O. Hesse, *J. prakt. Chem.*, [2] **65**, 91 (1902)] (*vide infra*).

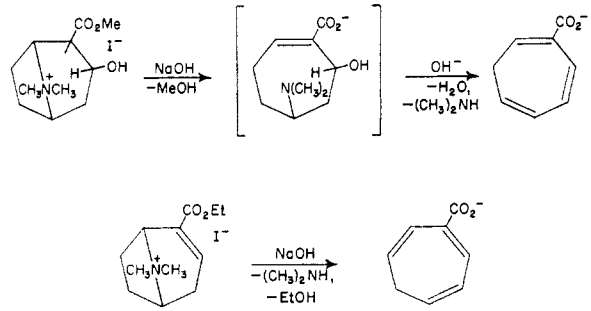
(11) A. Einhorn, *Ber.*, **20**, 1221 (1887).

(12) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 118.

(13) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 523 (1933).

(14) M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, *ibid.*, 2093 (1948).

(15) That dehydration precedes Hofmann elimination in ecgonine methyl ester methiodide appears unlikely because it undergoes the elimination reaction to dimethylamine and cycloheptatriene carboxylic acid more rapidly[6b] than the dehydrated analog, anhydroecgonine ethyl ester methiodide [C. Grundmann and G. Ottmann, *Ann.*, **582**, 163 (1953)]. The two reactions may proceed as indicated below (see, however, Grundmann and Ottmann, above).



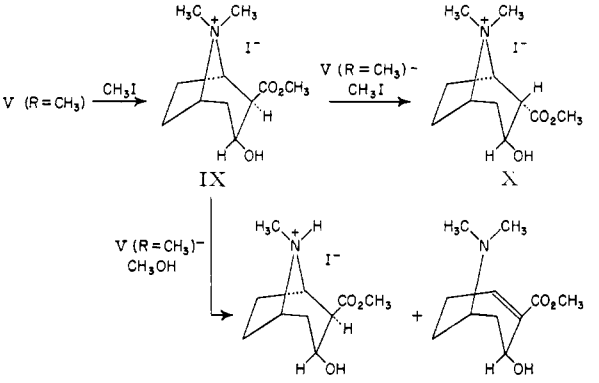
The facilitating action of the α- or C_2-H, whether *cis* or *trans*, is evident from the resistance of esters of dihydroxyanhydroecgonine and of α-ecgonine to Hofmann degradation [R. Willstätter, *Ber.*, **32**, 1635 (1899); **29**, 2216 (1896)].

a small quantity of trimethylamine or hydroxide ion. It is, therefore, probably a bimolecular (E-2) reaction and subject to the above discussed stereochemical restrictions.[14] Such an elimination reaction during formation of the methiodides of structures V and VII (R = CH_3) would be favored by the *trans* relation of the nitrogen and C_2-hydrogen and promoted at the beginning by the presence of unreacted ester. It is noteworthy that no hydriodide by-product is obtained from pseudoecgonine methyl ester and methyl iodide in methanol.[1] The rearrangement whereby ecgonine methyl ester and methyl iodide furnish pseudoecgonine methyl ester methiodide[1] can be similarly explained (*vide infra*).

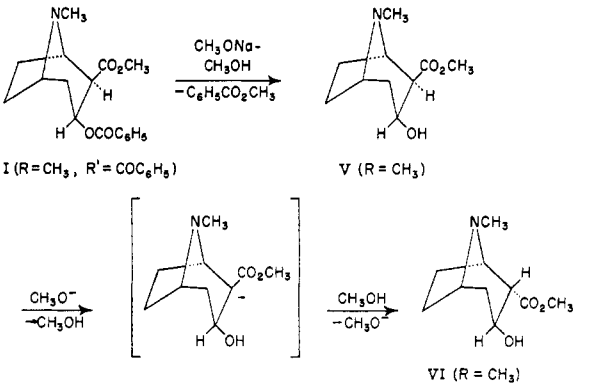
To summarize, the existing experimental data indicate that in ecgonine the carboxyl group is *cis* to the hydroxyl group and *cis* to the nitrogen atom. The hydroxyl group and nitrogen atom must then be *cis* to each other, and ecgonine must have structure V (R = H). The data indicate also that in pseudoecgonine the carboxyl group is *trans* to the hydroxyl group and to the nitrogen atom. Pseudoecgonine should therefore differ from ecgonine only in having a *trans* rather than a *cis* carboxyl group, and this inference is supported by above discussed nature of the ecgonine-pseudoecgonine transformation.[16] A brief account of this treatment was given earlier.[17]

The correctness of these deductions was established by proving the epimerizability of C_2 (structure I) and by determining the steric relation of the 3-benzoxy group of cocaine (I, R = CH_3, R′ = COC_6H_5) to the nitrogen atom using the method of acyl migration.

Willstätter's observation, that at room temperature ecgonine methyl ester combined with methyl iodide in methanol to give a mixture containing ecgonine methyl ester methiodide (IX) and a hydriodide salt and with methyl iodide alone to give pseudoecgonine methyl ester methiodide (X), has been confirmed. The pseudoecgonine methyl ester methiodide so obtained is identical with that got directly from pseudoecgonine methyl ester and methyl iodide as indicated by the melting points and specific rotations of the two preparations and by the melting point of their mixture. There appears to be no recorded example of epimerization of a secondary hydroxyl group of the kind present during methiodide formation, a type required by Willstätter's explanation of the isomerism of ecgonine and pseudoecgonine,[1,6] whereas, as earlier pointed out, epimerization of the α-carbon atom (C_2) of ecgonine methyl ester methiodide, promoted by the positively charged nitrogen atom and the presence of unreacted ecgonine methyl ester, accounts satisfactorily for the transformation. Moreover, it was found that the heretofore unidentified hydriodide salt is indeed that (XI) of ecgonine methyl ester (V = CH_3). The significance of the formation of the hydriodide salt was referred to earlier, and it is hoped to give a detailed report soon of the reaction of ecgonine methyl ester with methyl iodide under various conditions.



Furthermore, it was found that cocaine (I, R = CH_3, R′ = COC_6H_5) was converted by less than a tenth of a molar proportion of sodium methoxide in boiling methanol to pseudoecgonine methyl ester in 83% yield



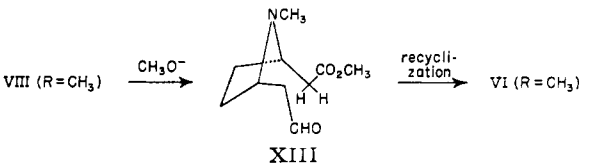
In this reaction the methoxide ion effects catalytic debenzoylation[18] and epimerization either in steps or simultaneously. The conditions of this reaction are considerably milder and more specific than those (33% aqueous potassium hydroxide at 100° for 24 hours)[2] necessary to convert ecgonine to pseudoecgonine. It was noted earlier that esters of the type *CHRR′CO_2R are readily racemized under such conditions and are much more labile than the corresponding carboxylate ions.[8,19]

(16) The biochemical evidence is not a disagreement with this conclusion. The naturally occurring tropane alkaloids with few exceptions contain a 3-acyloxy group. A given solanaceous plant usually makes only one configuration at C_3, *e.g.*, hyoscyamine and hyoscine which occur together in *Atropa belladonna* and *Datura stramonium*, and there appears to be no proved instance as yet of the coexistence in any plant of both configurations of a given 3-acyloxy group. Accordingly, one might expect cocaine (2-carbomethoxy-3-benzoxytropane) and tropacocaine (3-benzoxytropane) which occur together in *Erythroxylan coca* to have the same configuration at C_3. Tropacocaine has recently been found to have the *cis* relation of the benzoxy group and nitrogen atom.[1]

(17) S. P. Findlay, THIS JOURNAL, **75**, 1033 (1953). Compare, A. K. Bose and D. K. R. Chaudhuri, *Nature*, **171**, 652 (1953).

(18) M. Jones and A. Lapworth, *Proc. Chem. Soc.*, **30**, 141 (1914).

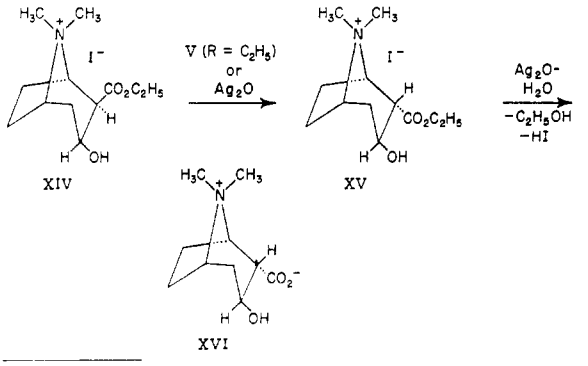
(19) It has been objected that inversion of ecgonine methyl ester at C_3 rather than at C_2 by sodium methoxide might conceivably occur through a kind of reversible dealdolization–realdolization process



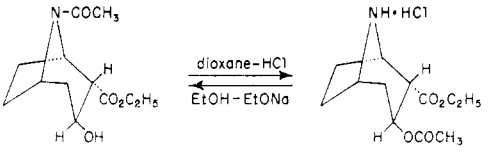
The failure to obtain all the possible isomers by this process is attributed to unfavorable equilibrium constants for their formation (referee's report). Unlike the epimerization explanation this conjecture appears to lack an analogy.

Finally, it was noticed that Hesse's ecgonine methylbetaine, prepared by reaction of ecgonine with methyl iodide and treating the product with silver oxide,[20] was different from Willstätter's ecgonine methylbetaine, obtained by shaking ecgonine ethyl ester methiodide (XIV) with silver oxide.[21] Hesse reported the specific rotation of his compound (−42.4°, water), but he unaccountably neglected to verify the melting point (278°) reported by Willstätter two or more years earlier for a compound of the same name or to remark on the difference in melting point of the hydriodides and chloroaurates of the two preparations. On repetition of Hesse's work it was found that his initial product was actually a mixture the principal component of which was ecgonine methyl ester hydriodide, an isomer of ecgonine methiodide. Furthermore, by the more direct method of Hesse pseudoecgonine methylbetaine (XVI) was obtained from pseudoecgonine and appears to be identical with Willstätter's betaine. In brief, although the preparation of ecgonine methylbetaine has been reported twice, it remains unknown. The simplest explanation of this final example of the ecgonine–pseudoecgonine transformation is once again epimerization of the C_2 of ecgonine ethyl ester methiodide (XIV) to give pseudoecgonine ethyl ester methiodide (XV), rather than of C_3 or of C_2 and C_3.[8,22]

This conversion of ecgonine to ecgonine methyl ester hydrodiode is not without analogy. Skraup observed that benzoylecgonine combines with methyl iodide to give benzoylecgonine methyl ester (cocaine) hydriodide, rather than benzoylecgonine methiodide,[23,24] and later Novy applied the method to prepare higher homologs of cocaine.[25] A relatively small amount of pseudoecgonine methyl ester hydriodide (about 5%) is obtained as a by-product in the reaction of pseudoecgonine with methyl iodide. The small yield here suggests that the carboxyl group is much less favorably located for the rearrangement than in ecgonine. Together with other evidence it suggests also that the rearrangement of alkylbetaines to dialkylamino esters proceeds unimolecularly as well as bimolecularly.[26]



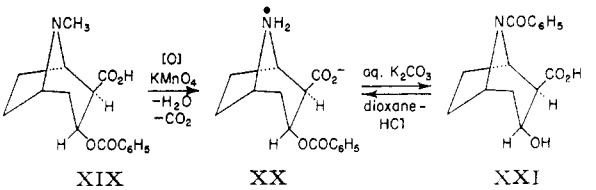
G. Fodor has shown that the monobenzoylated derivatives of *cis*-2-aminocycloalkanols readily undergo acyl migration whereas the *trans* isomers do not.[27] Applying this elegant method to the appropriate derivatives of ecgonine and pseudoecgonine, he determined that the hydroxyl and carboxyl groups are *cis* in the former compound and *trans* in the latter.[28] Moreover, he found that N-acetylnorpseudoecgonine ethyl ester (XVII) rearranged in dioxane solution containing hydrogen chloride to O-acetylnorpseudoecgonine ethyl ester hydrochloride (XVIII) which could be reconverted to the N-acetyl isomer by base[28]:



He concluded that pseudoecgonine has the *cis* relation of hydroxyl and nitrogen atom and therefore has structure VI (R = H). This agrees with one of the foregoing deductions.

However, he reported that N-acetylnoreegonine ethyl ester in dioxane solution containing hydrogen chloride was not isomerized to O-acetylnorecgonine ethyl ester hydrochloride and, furthermore, that the free amino acid liberated from Einhorn's benzoylnorecgonine hydrochloride[29] with base contained no detectable amount of the N-benzoyl isomer.[28] He inferred therefrom that ecgonine has the *trans* relation of hydroxyl group and nitrogen atom and therefore has structure VIII (R = H). This conclusion disagrees with the deduction made above concerning ecgonine.

To explain this contradiction a study of the chemistry of norecgonine was undertaken. In preparing the necessary precursor, O-benzoylnorecgonine (XX), it was noticed that the inadvertent use of insufficient acid in isolating the product caused the formation of oily by-products, which considerably lowered the yield of the desired compound and in one case furnished a crystalline substance unreported heretofore. After purification, the new compound melted at 163.5°, and elementary analysis indicated it to be an isomer of O-benzoylnorecgonine, $C_{15}H_{17}NO_4$. The suspicion that the new compound had been formed by rearrangement of this substance was confirmed. In aqueous potas-



(20) O. Hesse, *J. prakt. Chem.*, [2] **65**, 91 (1902).

(21) R. Willstätter, *Ber.*, **32**, 1635 (1899).

(22) (a) E. Biilmann and N. Berg, *Bull. soc. chim.*, [5] **1**, 1645 (1934). (b) E. Fischer, *Ber.*, **40**, 5000 (1907). (c) It is not certain whether this transformation occurred during the formation of the methiodide or in the subsequent treatment with silver oxide. The above discussed behavior of ecgonine methyl ester and the stability of the methiodide to boiling water[21] make the former explanation the more credible.

(23) Zd. H. Skraup, *Monatsh.*, **6**, 556 (1885).

(24) *Cf.*, L. F. Small and S. G. Turnbull, THIS JOURNAL, **59**, 1541 (1937); R. Pschorr, *Ann.*, **391**, 43 (1912); H. Rapoport, *J. Org. Chem.*, **13**, 714 (1948).

(25) F. G. Novy, *Am. Chem. J.*, **10**, 145 (1888).

(26) *Cf.*, R. Kuhn and F. Giral, *Ber.*, **68B**, 387 (1935).

(27) (a) G. Fodor and J. Kiss, *Nature*, **164**, 917 (1949); (b) *J. Chem. Soc.*, 1589 (1952).

(28) G. Fodor and O. Kovács, *ibid.*, 724 (1953).

(29) A. Einhorn, *Ber.*, **21**, 3029 (1888).

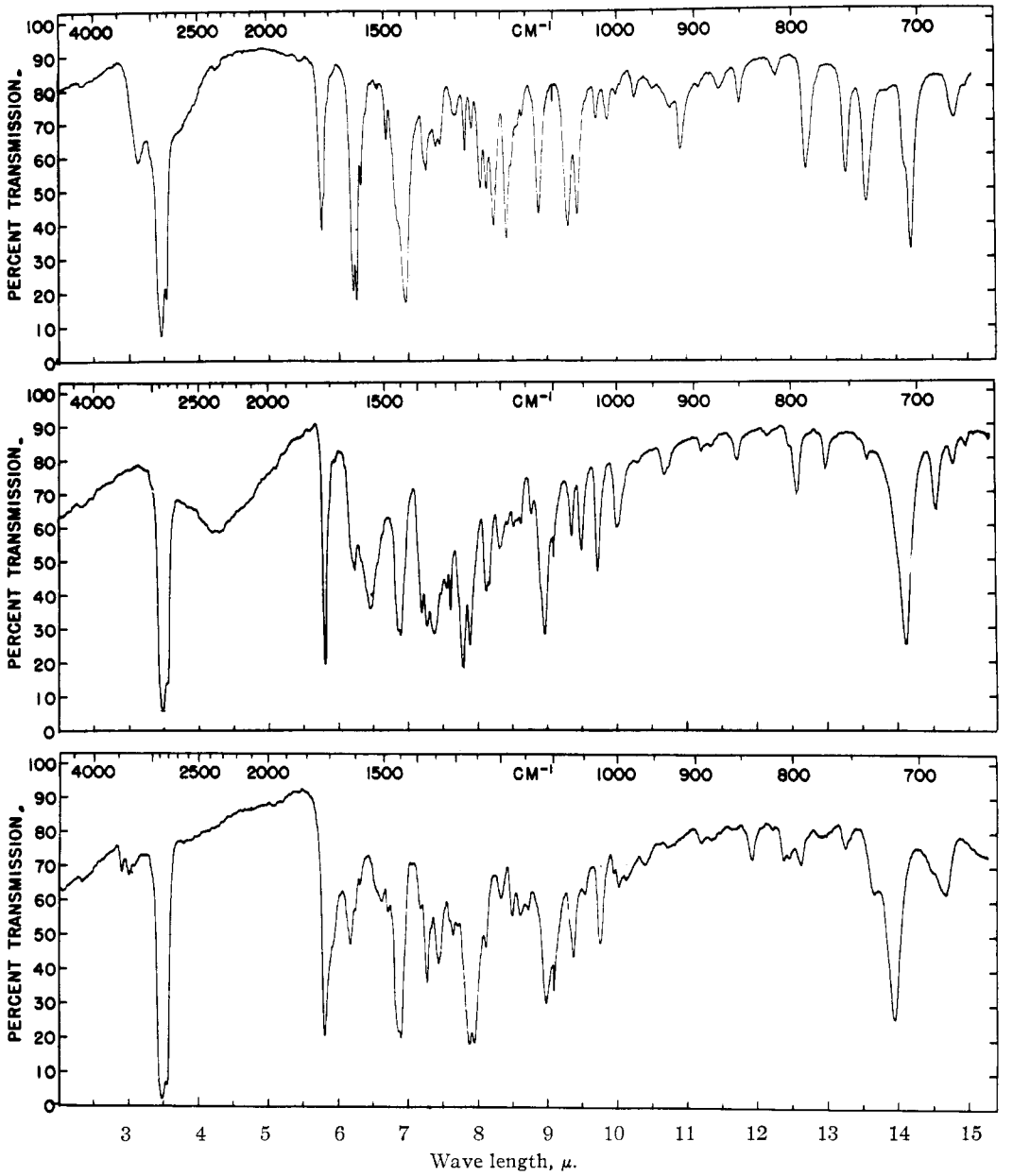


Fig. 1.—Infrared spectra (Nujol mulls): top, N-benzoylnorecgonine; middle, O-benzoylnorecgonine; bottom, benzoylecgonine.

sium carbonate O-benzoylnorecgonine undergoes internal acyl migration, the N-benzoyl isomer XXI, m.p. 163.5°, being formed. The process can be reversed by treating the dioxane solution of the N-benzoyl isomer with hydrogen chloride.[30] The N-benzoyl isomer is moderately acidic, the O-benzoyl isomer is almost neutral.

The identity of the N-benzoyl isomer was further established by comparing its infrared absorption spectrum in Nujol with those of benzoylecgonine and O-benzoylnorecgonine (Fig. 1). N-Benzoylnorecgonine has absorption maxima at 3.12 and 5.76 μ ascribable to a bonded hydroxyl and a carboxyl group, respectively, and a double maximum at 6.21 and 6.26 μ attributable to a N,N-dialkylated benzamide linkage.[31] O-Benzoylnorecgonine has broad weak absorption from *ca.* 3.65 to 5.5 μ assignable to NH_2^+ of a zwitterion[32] and maxima at 5.80 and 6.45 μ ascribable to an O-benzoyl linkage and to a carboxylate ion, respectively.

Both the interpretation of the general chemistry of cocaine derivatives and the evidence from epimerization and acyl migration studies therefore indicate that Fodor's structure for ecgonine (VIII, R = H) must be replaced by structure V(R = H). Cocaine itself is then 2β-carbomethoxy-3β-benzoxy-

(30) Some O → N acyl migrations occur almost instantaneously.[28] The comparative sluggishness of the rearrangement of O-benzoylnorecgonine and the failure of N-acetylnorecgonine to rearrange result presumably from steric hindrance.

(31) L. Fieser and A. Nickon, THIS JOURNAL, **74**, 5566 (1952).

(32) L. Larsson, *Acta Chem. Scand.*, **4**, 27 (1950).

tropane and pseudococaine 2α-carbomethoxy-3β-benzoxytropane.[33]

The third and fourth optically active cocaines and ecgonines have not yet been isolated. However, Willstätter obtained the racemate of a third ecgonine from the large-scale reduction of 2-carbomethoxytropinone.[1] This substance was readily dehydrated to racemic anhydroecgonine and so presumably has the *cis* relation of carboxyl and hydroxyl groups which permits the *trans* removal of water. Therefore, it very probably has structure VIII (R = H), and by the process of elimination the fourth ecgonine is VII (R = H). It is proposed that 2α-carboxy-3α-hydroxytropane (VIII, R = H) be called alloecgonine and 2β-carboxy-3α-hydroxytropane (VII, R = H) allopseudoecgonine. Their benzoylated methyl esters would be allococaine and allopseudococaine.

Miscellaneous Observations.—According to Einhorn benzoylnorecgonine melts at 230°.[29] The purest preparations obtained in this investigation melted about 250° (cor.). Although his observation was no doubt uncorrected, the discrepancy is so large as to indicate that his preparation was impure, the contaminant being very probably the N-benzoyl isomer.

The ready conversion of cocaine to pseudoecgonine methyl ester provides a new and better route to pseudoecgonine. Einhorn's preparations melted at 254 and 257°.[2,34] Pseudoecgonine is obtained quantitatively by boiling its methyl ester with water and melts at 275° (cor.).

A consideration of the specific rotations of derivatives of cocaine leads to the conclusion that the 2-*cis*–3-*cis* relation of substituents attached to the tropane ring results in levorotation whereas the 2-*trans*–3-*cis* relation of substituents produces dextrorotation.

Because they are β-hydroxy acids, ecgonine and corynanthic acid have some notable chemical similarities. Both are recovered unchanged from the acid hydrolysis of their esters, and both are epimerized by the alkaline hydrolysis of their esters.[9,35,36]

Experimental[37]

Pseudoecgonine Methyl Ester.—Dried cocaine (45.6 g., 0.150 mole) was dissolved in anhydrous methanol (200 ml.), a solution of sodium (0.30 g., 0.013 mole) in anhydrous methanol (50 ml.) added, and the mixture refluxed four hours. After standing overnight the mixture was shaken with benzene (250 ml.) and aqueous potassium bicarbonate (5 g. and 25 ml.), the precipitated salts filtered off, and the benzene–methanol solution dried over potassium carbonate. The organic phase was concentrated to 125 ml. on the steam-bath and a small quantity of insoluble matter (m.p. >285°) filtered off. The filtrate was concentrated *in vacuo* to a white crystalline mass. This largely dissolved in boiling ligroin (85–100°) (300 ml.) and on cooling **pseudoecgonine methyl ester** (24.0 g., 80%), m.p. 114–115.5°, separated. A small second crop (0.9 g., 3%) was obtained from the mother liquors. Extraction of the mother liquor from the second crop with dilute hydrochloric acid, extraction of the basified acid solution with ether, and removal of the solvent afforded about 2 g. of a colorless oil which was found to be a mixture of the methyl esters of ecgonine and pseudoecgonine.

The tan, ligroin-insoluble material (about 3 g.) was principally the alkali metal salts of pseudoecgonine.

Pseudoecgonine methyl ester binoxalate was prepared in and purified from methanol: small prisms, m.p. 190–191°.

Anal. Calcd. for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.61; N, 4.84. Found: C, 49.72; H, 6.66; N, 5.04.

Pseudoecgonine methyl ester, regenerated from the binoxalate and recrystallized from acetone, melts at 114–116° (reported 115[2] and 116°[1]) and has $[\alpha]^{20}D$ +22.8° (*c* 1.7, H_2O) (reported +19.5° (*c* 5, H_2O)).[1]

Pseudoecgonine methyl ester hydrochloride was prepared by treating the methyl ester with methanolic hydrogen chloride. It was recrystallized from methanol–acetone: irregular crystals, m.p. 209.5°; $[\alpha]^{20}D$ +23.4° (*c* 2.2, H_2O) (reported +23.7° (*c* 5, H_2O)).[1]

Ecgonine Methyl Ester.—Ecgonine (81 g.) was added to dry methanol (500 ml.) containing hydrogen chloride (100 g.) and the mixture, protected from moisture, was shaken frequently during 45 minutes whereby the granular amino acid was largely converted to the powdery hydrochloride. After standing overnight the mixture was gently refluxed 3 hours during which period the white hydrochloride gradually dissolved and about 70% of the hydrogen chloride was lost. More hydrogen chloride (40 g.) was added and the mixture refluxed another hour. The solvent was removed *in vacuo* and traces of HCl and methanol by storing *in vacuo* over potassium hydroxide: 100 g. (101%). The crude product was recrystallized from methanol (120 ml.): 46 g., m.p. 213.5° (first crop); 24 g., m.p. 212.5° (second crop); 11 g., m.p. 213° (third crop). Recrystallized to constant melting point from ethyl alcohol or by adding hot acetone to a hot methanol solution of the salt, **ecgonine methyl ester hydrochloride** was obtained as colorless crystals, m.p. 215° (reported[38] 212°); melting point of a mixture with the pseudo isomer, 190°. The anhydrous form of the ester is obtained by drying *in vacuo* at room temperature and melts at 222°; $[\alpha]^{20}D$ −50° (*c* 1, CH_3OH).

Anal. Calcd. for $C_{10}H_{18}ClNO_3$: C, 50.95; H, 7.70. Found: C, 50.82; H, 7.89. Calcd. for $C_{10}H_{18}ClNO_3 \cdot 1H_2O$: C, 47.33; H, 7.94. Found: C, 47.23; H, 7.86.

Ecgonine methyl ester chloroaurate was prepared in methanol in which it is quite soluble and precipitated by adding water: yellow flakes, m.p. 114°.

Ecgonine methyl ester was obtained by adding the hydrochloride to excess aqueous potassium carbonate and extracting with benzene or chloroform. The latter solvent has the disadvantage that it slowly reacts with the ester to give the ester hydrochloride which precipitates. After drying with potassium carbonate, the extract was concentrated and the ester distilled *in vacuo*. **Ecgonine methyl ester** is an almost colorless oil which has practically no odor just after distillation. It boils at 84° (0.5 mm.) and 104–106° (2.0–2.3 mm.) and has $n^{19}D$ 1.4886, $d^{19}D$ 1.1451 ± 0.0005, and $[\alpha]^{20}D$ −12.3° (*c* 2, abs. methanol). It is hygroscopic, and the water absorbed causes slow hydrolysis as indicated by the separation of ecgonine.

Pseudoecgonine Methyl Ester Methiodide (a) **from Pseudoecgonine Methyl Ester.**—The ester (0.5 g.), m.p. 114–115°, was mixed at 0° with methyl iodide (1.0 ml.) and stored in the refrigerator overnight. The white, granular product after being washed with cold methanol melted at 214–215°. Recrystallized from methanol it was obtained as long needles, m.p. 215–216°. Similar results were obtained when methanol was employed as solvent for the reactants. The yield in both reactions was nearly quantitative. The methiodide had $[\alpha]^{20}D$ +11.2° (*c* 2, methanol) (reported[1] +11.3°).

(b) **From Ecgonine Methyl Ester.**—Methyl iodide (0.2 ml.) was added to ecgonine methyl ester (0.5 g.) at room temperature. The mixture quickly became turbid, then warm, and finally solidified to a yellowish white mass. This was recrystallized from methanol from which it sepa-

(33) This nomenclature for indicating the three-dimensional structure of substituted tropanes has been proposed by G. Fodor and K. Nădor [*J. Chem. Soc.*, 721 (1953)]. Alternatively, cocaine may be called, the nitrogen atom being used as the point of reference, 2-*cis*-carbomethoxy-3-*cis*-benzoxytropane [S. P. Findlay, THIS JOURNAL, **75**, 4624 (1953)].

(34) A. Einhorn and A. Marquardt, *Ber.*, **23**, 979 (1890); *cf.* C. Liebermann and F. Giesel, *ibid.*, **23**, 926 (1890).

(35) L. Marion in "The Alkaloids" (Edited by R. H. F. Manske and H. L. Holmes), Academic Press, Inc., New York 10, N. Y., 1952, p. 419.

(36) M.-M. Janot, R. Goutarel, A. LeHir, M. Amin and V. Prelog, *Bull. soc. chim.*, 1085 (1952).

(37) All melting points are corrected.

(38) A. Einhorn and O. Klein, *Ber.*, **21**, 3335 (1888).

rated as long, fine needles: m.p. 211–212°. The yield was nearly quantitative. Recrystallized from methanol again, it melted at 216–216.5°. The melting point of a mixture with pseudoecgonine methyl ester methiodide, obtained as described above, was 216–216.5°. It had $[\alpha]^{20}D$ +11.3° (*c* 1.0, methanol).

Anal. Calcd. for $C_{11}H_{20}INO_3$: C, 38.72; H, 5.91; I, 37.2. Found: C, 38.72; H, 5.88; I, 37.4.

The Reaction of Ecgonine Methyl Ester with Methyl Iodide in Methanol.—Ecgonine methyl ester (9.0 g.) was dissolved in absolute methanol (18.0 ml.) and methyl iodide (3.5 ml.) added to the mixture at room temperature. The mixture gradually turned yellow and overnight deposited crystalline material (4.0 g., m.p. 200–203°). After three recrystallizations from methanol long, hair-like needles of ecgonine methyl ester hydriodide were obtained: m.p. 211.5–212.5°; $[\alpha]^{20}D$ −38.3° (*c* 1, CH_3OH).

Anal. Calcd. for $C_{10}H_{18}INO_3$: C, 36.71; H, 5.54; I, 38.79. Found: C, 37.19; H, 5.76; I, 38.98.

A mixture of the hydriodide and excess aqueous potassium carbonate was extracted with ether and the dried extract treated with ethereal hydrogen chloride. The voluminous precipitate had a melting point of 222° and after recrystallization from alcohol melted at 214°. The melting point of its mixture with authentic **ecgonine methyl ester hydrochloride** was not depressed.

The filtrate from the crude hydriodide was concentrated to about half volume and kept at 5°. A large yellowish precipitate (8.7 g.) was obtained which appeared to be a mixture. After two recrystallizations from methanol the white product melted at 162–175°.[1] A small proportion was extractable with chloroform from aqueous potassium carbonate. This fraction was presumed to be ecgonine methyl ester methiodide contaminated with the foregoing hydriodide and perhaps other products.

Anal. Calcd. for $C_{11}H_{20}INO_3$: C, 38.72; H, 5.91. Found: C, 39.16; H, 6.10.

The Reaction of Ecgonine with Methyl Iodide.[20]—Ecgonine (15.0 g.) was dissolved in absolute methanol (30 ml.) and to the refluxing solution was added methyl iodide (10 ml.) in methanol (10 ml.). The addition was completed in five minutes. After refluxing the mixture 2.5 hours (some product began to separate after about 1 hour), the hot solution was filtered from the white precipitate (fraction I) and cooled to 0°. The crystalline product which separated was collected (fraction II) and by successive concentrations of the mother liquors four additional fractions were obtained.

Fraction	Wt., g.	M.p., °C.	Analyses, %
I	8.2	219–220	C, 37.83; H, 5.83; I, 36.81
II	5.4	218.5–219	C, 37.50; H, 5.63
III	1.4	214–215	C, 37.72; H, 5.85; I, 36.61
IV	0.8	236–237	C, 43.47; H, 6.23; I, 25.82
V	0.73	190–196	
VI	1.7	115–210	
Residue	1.5		

Fraction I was heated with alcohol (150 ml.) and a small quantity of insoluble material filtered off. The filtrate furnished about 5.5 g. of crystalline material, m.p. 220.5–221°. This (3.0 g.) was added to excess aqueous potassium carbonate and the mixture extracted with ether (3 × 50 ml.). After drying the extract and removing the solvent, **ecgonine methyl ester** (1.3 g.) remained. This was identified as the hydrochloride. Fractions I to III appear therefore to be composed largely of ecgonine methyl ester hydriodide. The other product or products have not yet been identified. When fraction I in aqueous solution is shaken with a slight excess of freshly prepared silver oxide the principal product is **ecgonine**, m.p. 202.5–203°, $[\alpha]^{19}D$ −45.4° (*c* 2, H_2O) (reported −45.4° (H_2O)).[39]

Pseudoecgonine.—A mixture of pseudoecgonine methyl ester (4.0 g.), m.p. 114.5–116°, and water (25 ml.) was boiled 2.5 hours. The water and methanol were then removed *in vacuo;* the residue was practically pure pseudoecgonine: 3.7 g. (100%), m.p. 267–268°. It was recrystallized from alcohol: small, stout prisms, m.p. 272° (275° *in vacuo*, dec.), $[\alpha]^{20}D$ +22.7° (*c* 1 or 2.5, H_2O).

This compound was also prepared by the directions of Einhorn and Marquardt who reported a quantitative yield.[2] Ecgonine (15.0 g.) furnished pseudoecgonine hydrochloride (9.9 g., 55%), m.p. 243.5° (reported[2] 236°). An additional 6.3 g. which appeared to be a mixture of the hydrochlorides of ecgonine and pseudoecgonine was recovered from the mother liquor. On treatment with silver oxide the hydrochloride (12 g.) furnished pseudoecgonine (5.3 g., 53%), m.p. 273° dec., and less pure material (1.8 g.) melting at 261°. From the mother liquors was obtained a light brown sirup (~3 g.) which partially crystallized on keeping.

Pseudoecgonine Methiodide.—Pseudoecgonine (1.8 g.) was refluxed with a mixture of methanol (25 ml.) and methyl iodide (5.0 ml.) four hours. Nearly all of the pseudoecgonine which, in contrast to its methiodide, is sparingly soluble in methanol had dissolved after two hours. After keeping at room temperature the yellow solution was decanted from a small amount of precipitate and evaporated *in vacuo* to a gum. This was dissolved in boiling alcohol; pseudoecgonine methiodide melting at 245–246° separated on cooling. A second crop also was obtained. Its melting point decreases on recrystallization and its composition indicates a loss of hydrogen iodide. It was purified for analysis by dissolving in alcohol, adding a small quantity of 47% hydriodic acid which decolorized the solution, cooling, and diluting with ether which caused reappearance of the yellow color: small, slender needles, m.p. 235–236° (reported[21] 238°).

Anal. Calcd. for $C_{10}H_{18}INO_3$: C, 36.71; H, 5.54; I, 38.79. Found: C, 36.46; H, 5.34; I, 38.80.

The mother liquors from the second crop were concentrated to a brown sirup which was added to excess aqueous potassium carbonate. Extraction with ether (3 × 50 ml.) and removal of the solvent from the dried extracts afforded a yellow oil which largely crystallized when seeded with **pseudoecgonine methyl ester.** The crude product was purified from acetone: 0.1 g. of prisms, m.p. 113–115°.

Pseudoecgonine Methylbetaine.—This compound was prepared by shaking an aqueous solution of pseudoecgonine methiodide with silver oxide.[20] It was purified from alcohol: small, rectangular prisms, m.p. 302–306° (evac. tube), $[\alpha]^{20}D$ +28.2° (*c* 1.9, H_2O).

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.27; H, 8.60. Found: C, 60.61; H, 8.28.

Prepared by Willstätter's method[21] from pseudoecgonine methyl ester methiodide, the betaine melted at 304° (evac. tube) and had $[\alpha]^{20}D$ +29° (*c* 1.7, H_2O). In an open tube it melted at 282° (reported 278°).[21]

Pseudoecgonine methylbetaine chloroaurate was prepared in and purified from water: shiny yellow platelets, m.p. 217°.[21]

Benzoylecgonine.—Cocaine (25.0 g.) was boiled vigorously in water (200 ml.) until the oily base had dissolved (two hours). After keeping in the cold the crystalline product was collected: 16.4 g. of pure benzoylecgonine tetrahydrate. Evaporation of the mother liquors gave two additional crops. The anhydrous form was obtained by storing the hydrate *in vacuo* over calcium chloride and potassium hydroxide: 13.2 g. (55%), m.p. 199–201° and 4.0 g. of less pure material, m.p. 197.5–199°. According to Einhorn, when cocaine is boiled about 10 hours with water, benzoylecgonine is obtained in quantitative yield.[40]

The Permanganate Oxidation of Benzoylecgonine.—

$$C_{16}H_{19}NO_4 + 2KMnO_4 \longrightarrow C_{15}H_{16}NO_4K + 2MnO_2 + KHCO_3 + H_2O$$

A solution of potassium permanganate (6.56 g.) in water (250 ml.) was added dropwise during 155 minutes to a stirred solution of anhydrous benzoylecgonine (6.00 g.) in water (1 l.). After keeping overnight methanol (15 ml.) was added and the mixture stirred one hour. To facilitate removal of the manganese dioxide the mixture was stirred with charcoal and celite before filtering. The colorless filtrate was treated with 55.5 meq. of hydrochloric acid and evaporated to dryness *in vacuo*. Lingering traces of water and acid were largely removed from the residue by storing *in vacuo* over potassium hydroxide. The residue was boiled with absolute alcohol (50 ml.), the potassium chloride (2.1 g.) filtered off, and the filtrate concentrated to about 35 ml.

(39) C. Liebermann, *Ber.*, **21**, 2342 (1888).

(40) A. Einhorn, *ibid.*, **21**, 47 (1888).

in vacuo. The precipitate which began to separate during the evaporation was augmented by storing the mixture at 0° before filtering: 4.10 g. of crude **O-benzoylnorecgonine hydrochloride**, m.p. 214–216°. By diluting the filtrate with dry ether second (0.6 g.) and third (0.2 g.) crops were obtained. The hydrochloride was recrystallized twice from absolute alcohol and dried 7 hours at 77° for analysis: short, small prisms, m.p. 219–221°; $[\alpha]^{20}D$ −58.8° (*c* 1, H_2O).

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.81; Cl, 11.37. Found: C, 58.02; H, 5.81; Cl, 11.49.

When the aqueous filtrate from the manganese dioxide is treated with an amount of hydrochloric acid proportionately less than that noted above, the fraction of non-crystalline by-products is increased and from this little free O-benzoylnorecgonine can be isolated. In a modification of the above procedure a solution of potassium permanganate (9.80 g.) in water (450 ml.) was added all at once to a solution of anhydrous benzoylecgonine (9.00 g.) and potassium carbonate (4.30 g.) in water (1.80 l.). After keeping 16 hours, the manganese dioxide was filtered off and hydrochloric acid (94 meq.) added. The product was isolated as above described. By concentration of the alcoholic extract to about 25 ml. a small amount of **O-benzoylnorecgonine** (0.5 g.) was obtained. The solvent was removed from the filtrate and the residue (about 10 g.) made acid to congo red with hydrochloric acid. After drying two days *in vacuo* over potassium hydroxide, the mixture was taken up in absolute alcohol (10 ml.) and diluted with ether to slight turbidity. By keeping overnight at 5° a small quantity of crystalline material and a relatively large amount of oil was obtained. By further manipulation second and third crops were obtained; total yield of crude product: about 2 g. After recrystallization from absolute alcohol it melted at 161.5° (see **N-benzoylnorecgonine**). The remainder of the product in which some benzoic acid was detected was set aside.

N-Benzoylnorecgonine.—The product melting at 161.5° was recrystallized from absolute alcohol and from dioxane for analysis. From the latter solvent it separates as shiny flakes, m.p. 163–163.5°, $[\alpha]^{20}D$ 0.0 (*c* 2, H_2O), −17.7° (*c* 2.8, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.24; N, 5.09. Found: C, 65.66; H, 6.19; N, 4.87.

O-Benzoylnorecgonine.—According to Einhorn when benzoylnorecogonine hydrochloride is heated in ammoniacal solution, the initially formed ammonium salt decomposes and one obtains, as final product, benzoylnorecgonine, m.p. 230°.[25] Here it was found that, when a solution of benzoylnorecgonine hydrochloride is treated with excess 3 *N* ammonia at room temperature, O-benzoylnorecgonine, m.p. 242°, precipitates at once. The free base was further purified by two recrystallizations from water in which it is not very soluble: small, stout, tan prisms, m.p. 250° dec.; $[\alpha]^{20}D$ −47° (*c* 0.9, H_2O).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.24; N, 5.09. Found: C, 65.30; H, 6.24; N, 5.20.

N-Benzoylnorecgonine from the O-Benzoyl Isomer.—O-Benzoylnorecgonine (0.275 g.) was dissolved in water containing anhydrous potassium carbonate (0.207 g.) and the solution diluted to 10.0 ml. After keeping 7 days at room temperature the *p*H was reduced to 3.10 with normal hydrochloric acid and the solution concentrated to dryness *in vacuo*. The residue (0.45 g.) was leached with boiling chloroform and the soluble material recovered by removing the solvent *in vacuo:* 0.25 g. of gummy, white crystals. After two recrystallizations, one from absolute alcohol–ether and one from absolute alcohol, the product melted at 163–163.5° and its mixture with authentic N-benzoylnorecgonine at 163–163.5°.

O-Benzoylnorecgonine from the N-Benzoyl Isomer.—N-Benzoylnorecgonine (0.30 g.) was dissolved in hot dioxane (4.0 ml.) and dry hydrogen chloride (0.44 g.) added. The mixture was heated 1 hour at 100°, more hydrogen chloride added, and heating continued another hour. During the second hour precipitation began. After two days at room temperature the **O-benzoylnorecgonine hydrochloride** was collected: 0.3 g., m.p. 217.5–219°. A small second crop also was obtained. The hydrochloride was dissolved in water (0.5 ml.) and treated with excess 3 *N* aqueous ammonia at room temperature. The resulting clear solution quickly deposited colorless crystals when scratched with authentic O-benzoylnorecgonine: m.p. 242° dec. These were recrystallized from water: m.p. 248°; mixed m.p. with authentic material: 248°.

Infrared Measurements.—All measurements were made with a Perkin–Elmer model 21 double beam spectrometer with sodium chloride optics. The suspensions of the compounds in Nujol were prepared and their spectra obtained in the usual manner.

***p*H Measurements.**—Hydrogen ion concentrations were measured with a Beckman Model G Glass Electrode *p*H Meter at 20°. The *p*H of approx. 0.0319 *M* aqueous O-benzoylnorecgonine hydrochloride was 2.20; of 0.0419 *M* aqueous O-benzoylnorecgonine, 5.81; of 0.0375 *M* aqueous N-benzoylnorecgonine, 3.20; and of an aqueous solution 0.050 *M* with respect to both O-benzoylnorecgonine and its hydrochloride, 2.60.

Acknowledgments.—The author is indebted to the Analytical Services Laboratory, directed by Dr. William C. Alford, for the analytical data herein reported and to Mrs. Alma Hayden for the infrared measurements. He is also obliged to Mr. Theodore D. Perrine of this Institute for the ecgonine used in this investigation.

BETHESDA 14, MARYLAND