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SYNTHESIS OF IPECACUANHA ALKALOIDS*

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Abstract—Alkaloids of ipecacuanha are plant bases of a complex chemical structure. The structures of emetine and related alkaloids have been extensively studied. This paper summarises the work carried out by the present authors in the course of many years and deals with the procedures of building up particular groups characteristic of these alkaloids and their parent substances. The investigation has led to the assignment of the structures and to the syntheses of isomeric and stereoisomeric emetines and related alkaloids such as O-methylpsychotrines, psychotrine, cephaeline, emetamine and a number of their analogues. The syntheses of alkaloids of the *iso*quinoline, quinoline, and indole series have been shown to be interconnected and have been effected from the same parent compounds and by similar conversions.

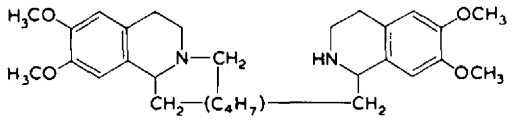
ALKALOIDS of the *iso*quinoline group are of great theoretical and practical interest, including a number of important compounds widely used in medicine, such as morphine and related alkaloids, *d*-tubocurarine and many others. The study of the chemical structure and conversions of *iso*quinoline alkaloids was therefore deemed to be of great theoretical value, and it has helped to establish a genetic and chemical relationship between alkaloids of different groups, for example, between the derivatives of *iso*quinoline, quinoline and indole.

A group of chemically related alkaloids produced from the tropical plant Ipecacuanha, namely emetine, O-methylpsychotrine, psychotrine, cephaeline and emetamine are *iso*quinoline derivatives.

Synthesis of isomeric and stereoisomeric emetines

Emetine was first discovered in 1817[1] and in 1879 Podvisotsky obtained it as a pure substance;[2] its empirical formula was only established in 1914, because of the extremely complicated procedure involved in purifying the alkaloid. The crystalline base of emetine was not produced until 1953.[3]

The study of various reactions of emetine carried out by several investigators showed that its molecule consists of two tetrahydro*iso*quinoline nuclei linked by a group of seven carbon atoms.



I

The further elucidation of the structure of emetine proved to be very difficult. The suggested formulae did explain many emetine reactions, but none of them fully accounted for its properties.

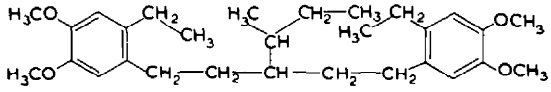
* Translated by A. L. Pumpiansky, Moscow.

[1] J. Pelletier and Magendie, *Ann. Chim. Phys.* [2], **4**, 172 (1817).

[2] V. Podvisotsky, New pharmacological and chemical investigations of the ipecacuanha root alkaloid emetine. (1879).

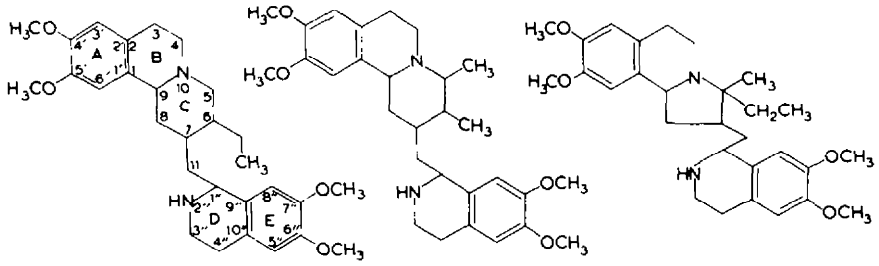
[3] G. E. Foster and G. W. Nargrove, *J. Pharm. Pharmacol.* **5**, 480 (1953).

In 1948–1950 many investigations were published of attempts to elucidate the structure of the central part of the emetine molecule.[4] The products of degradation of emetine, produced by exhaustive methylation, were investigated and synthesised, and many compounds derived from emetine and other related alkaloids were obtained. These investigations determined the structure of the hydrogenated product obtained by exhaustive methylation of emetine (II) that fully retained the nitrogen-free alkaloidal skeleton.



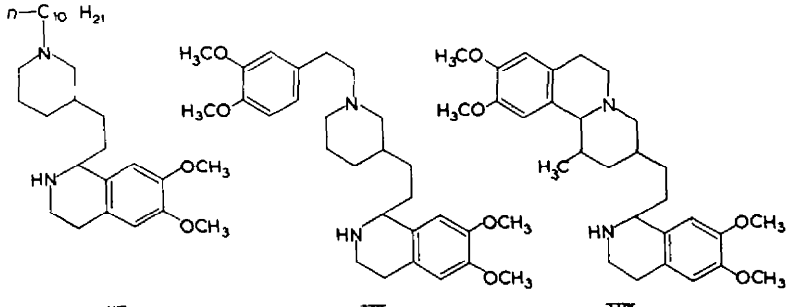
II

This structure suggested three probable formulae of emetine, namely (III), (IV) and (V), as shown:



III IV V

On the basis of investigations of *iso*quinoline compounds with structures close to that expected for emetine such as 1-β-[(*N*-decyl)-3′-piperidyl]ethyl-6:7-dimethoxy-1:2:3:4-tetrahydro*iso*quinoline[5] (VI), 1-β-[*N*-β-(3″:4″-dimethoxyphenyl)ethyl-3′-piperidyl]ethyl-6:7-dimethoxy-1:2:3:4-tetrahydro*iso*quinoline[6] (VII), 1″-(4′:5′-dimethoxy-8-methyl-3:4:5:6:7:8-hexahydrobenzo-1′:2′:1:2-quinolizine-6-ethyl)-6″:7″-dimethoxy-1″:2″:3″:4″-tetrahydro*iso*quinoline[7] (VIII)



VI VII VIII

[4] E. Späth and M. Pailer, *Mh. Chem.* **78**, 348 (1948); M. Pailer and L. Bilck, *Mh. Chem.* **79**, 127 (1948); M. Pailer, *Mh. Chem.* **79**, 331 (1948); M. Pailer and K. Porschinski, *Mh. Chem.* **80**, 94 (1949).

[5] R. S. Livshits, M. S. Bainova, S. D. Kuprianova and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXIII**, 522 (1953).

[6] R. S. Livshits, M. S. Bainova, A. J. Gurevich and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXIII**, 525 (1953).

[7] R. P. Evstigneeva, Dissertation "The Synthesis of the alkaloid emetine" (1950); L. I. Zakharkin and N. A. Preobrazhensky. *Zh. Obshch. Khim.* **XXIII**, 153, 518 (1953).

Formula (III) was postulated as the most probable for the alkaloid and a synthetical investigation was made.

Robinson came to this conclusion, starting from the structural and genetic relationship of the alkaloids of the *iso*quinoline group.[8]

Emetine was found to have the postulated structure (III), since the destructive degradation of emetine resulted in the isolation of the central part of the molecule as β-ethyl-γ-methylpyridine. Final confirmation of the emetine structure was obtained by the synthesis effected in 1950.[9]

Several routes were studied as shown in the general scheme (see p. 226):

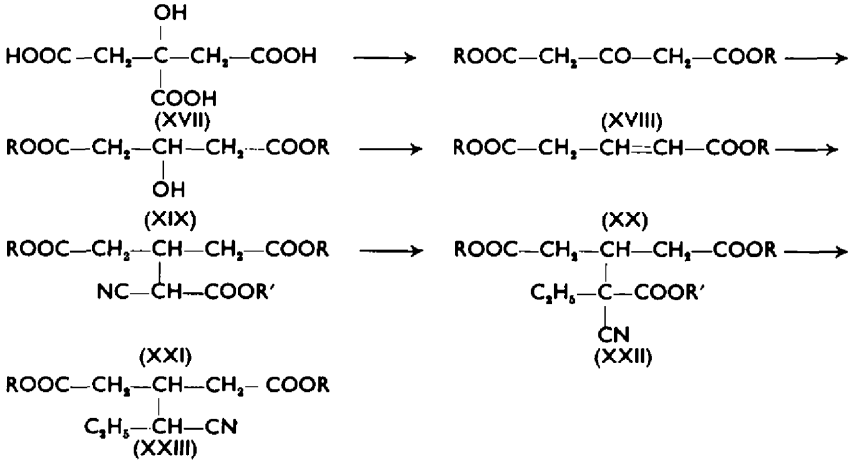
It was decided to make use of a starting compound whose structure would predetermine the structure of the whole central part of the alkaloid molecule, that is, of that part of the molecule requiring experimental evidence. The structure of this parent compound corresponded to the general formula (IX). There being the necessary and suitably arranged functional groups —COOR, —CH_2Br, —$CH(OR)_2$ and —CN in the structure (IX), the condensation of this compound with homoveratrylamine permitted the building up of the quinolizine and *iso*quinoline systems involved in the structure of emetine. As starting substances for the central part of the emetine molecule, the following compounds were synthesised:

(a) ethyl β-(α'-bromomethyl)propylglutarate (IX; Z = CH^2Br);[10] m.p.132·5–133·5°

(b) β-(α'-diethylacetal)propylglutaric acid anhydride (IX, Z = $C(H)(OC_2H_5)_2$);[11] b.p. 155–157°/4 mm.

(c) methyl and ethyl β-(α'-cyano)propylglutarates (IX; Z = CN).

The compound that proved to be the most convenient for synthesising emetine, its isomers and other ipecacuanha alkaloids was (IX) with Z = CN, synthesised as follows:

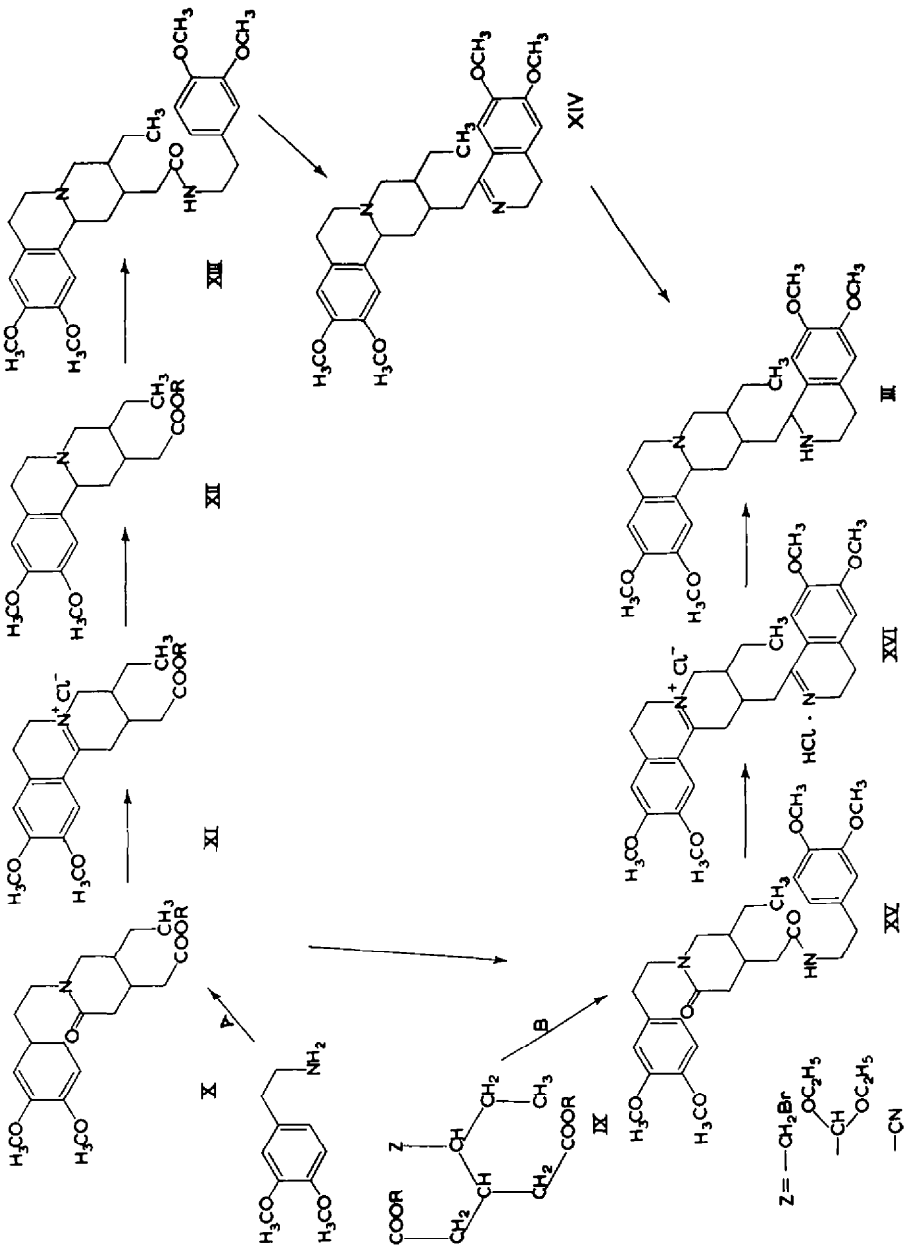


[8] R. Robinson, *Nature, Lond.* **162**, 155 (1948).

[9] R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova and N. A. Preobrazhensky, *Dokl. Akad. Nauk. SSSR* **75**, 539 (1950); *Zh. Obshch. Khim.* **XXII**, 149 (1952).

[10] L. I. Zakharkin and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXII**, 1890 (1952).

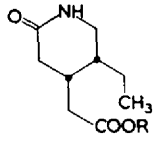
[11] M. S. Bainova, R. P. Evstigneeva, R. S. Livshits, K. K. Kusmina and N. A. Preobrazhensky, *Zh. Obshch. Khim.* **XXIII**, 149 (1953).



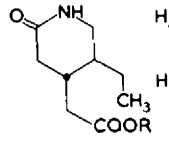
The chief intermediate used in the syntheses was ethyl glutaconate (XX; R = CH_3, C_2H_5), obtained from citric acid (XVII) via acetonedicarboxylic acid (XVIII; R = H), its esters (XVIII; R = CH_3, C_2H_5), ethyl and methyl β-hydroxyglutarates (XIX; R = CH_3, C_2H_5) and ethyl and methyl β-acetoxyglutarates. The glutaconates were condensed with ethyl cyanoacetate to give (XXI; R = R′ = C_2H_5), b.p. 182–183°/3 mm, and (XXI; R = CH_3, R′ = C_2H_5), 158–159°/2 mm. After alkylation of (XXI) with ethyl halide we obtained (XXII; R = R′ = C_2H_5), b.p. 189–190°/3 mm, (XXII; R = CH_3, R′ = C_2H_5), (XXI; R = CH_3, R′ = C_2H_5), b.p. 156–158°/1 mm, and (XXII; R = R′ = CH_3), b.p. 150–152°/1 mm.

The selective saponification of one of the ester groups to (XXII) followed by decarboxylation resulted in (XXIII; R = C_2H_5), b.p. 139–140°/2·5 mm, (XXIII; R = CH_3), 126·5–127°/1 mm. The reductive condensation of (XXIII) with homoveratrylamine (route A) in the presence of Raney nickel led to the addition of the latter compound to the nitrile group accompanied by the elimination of ammonia.

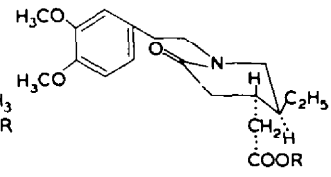
Simultaneously, the secondary amino group produced reacted with one of the carboalkoxy groups to yield ethyl and methyl *N*-(β-(3′:4′-dimethoxyphenyl)-ethyl)-δ-ethyl-α-piperidone-γ- acetates (X; R = C_2H_5 and R = CH_3), b.p. 200·5–202·5°/0·15 mm and 210–211°/0·35 mm, respectively. With the main reaction a side-reaction took place to give non-alkylated piperidones (XXIVa), (XIVb) and dihomoveratrylamine.



XXIVa



XXIVb



XXV

The usual ratio of alkylated to non-alkylated piperidones was 6:1 or 5:1. The yield of alkylated piperidone amounted to about 30 per cent. Piperidone (XXIV) was isolated in two stereoisomeric forms (a and b). Piperidone (X) should also have two isomeric forms, but all attempts to isolate the second isomer in a pure state failed. The substituent at the nitrogen seemed to favour the formation of one isomer only. As far as conformational analysis was concerned, the most favourable transform for the N-substituted piperidone (X) was apparently that with equatorial substituents (XXV).

Piperidone (X) was then cyclised to the chloride of the quaternary base (XI), with phosphorus oxychloride, pentachloride and pentoxide used as reagents. The further reduction of (XI) led to ethyl and methyl 4′:5′-dimethoxy-6-ethyl-3:4:5:6:7:8-hexahydrobenzo-(1:2:1′:2′)-quinolisyl-7-acetates (XII).

Hydrogenation of the chloride of the quaternary base (XI) was stereo-oriented, depending on the catalyst and the pH of the medium used. The above described synthesis resulted in the following three isomeric quinolizine esters[12]:

(*A*) An isomer with the melting point of the amorphous hydrochloride 177·5–179·5° and that of the crystalline hydrate 195–196°, obtained on hydrogenation in the presence of platinic oxide in acidic media (XII; R = C_2H_5).

[12] R. P. Evstigneeva, *Zh. Obshch. Khim.* XXVIII, 2458 (1958).

(*B*) An isomer with the melting point of its amorphous hydrochloride. 171·5–173·5° and that of the crystalline hydrate 194–196°, produced when hydrogenating in the presence of platinic oxide in neutral media (XII; $R = C_2H_5$).

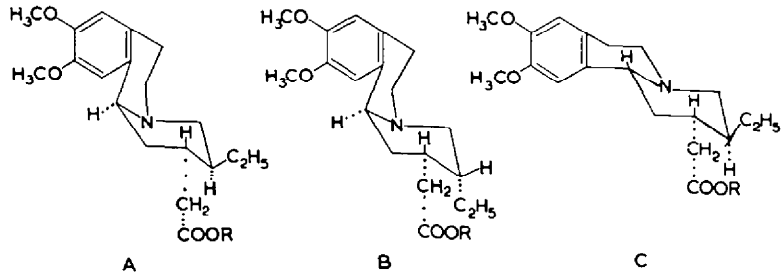
(*C*) An isomer with the melting point of its amorphous hydrochloride 175–179° and that of its crystalline hydrate 193·5–194·8°, obtained by hydrogenation in the presence of Raney nickel in neutral media (XII; $R = C_2H_5$).

It is to be noted that the esters of the quinolizine derivative of (XII) are extremely difficult to investigate.

The bases are isolated as oils. The salts of the anhydrous base with mineral and organic acids are amorphous. The isomeric esters have been identified as hydrochlorides, then converted into crystalline hydrates by adding a small amount of hydrochloric acid, followed by careful removal of the latter *in vacuo* and recrystallisation from alcohol.

The isomers produced are very similar in properties, but exhibit sharp depression of the mixed melting point of their hydrochlorides. Their ultra-violet absorption spectra proved to be almost identical.

The isomers appear to have the following configurations:



A B C

Hydrogenation with nickel catalyst proceeds with isomerisation also observed in distilling unstable bases of (XII). Heating with homoveratrylamine at 180–200° converts the stereoisomeric quinolizine esters (XII A), (XII B) and (XII C) into their respective amides with very similar properties, m.p. 144–145° (XIII A), 147·5–148·5° (XIII B) and 144–146·5° (XIII C), but showing depression of their mixed melting points.

Amides (XIII A), (XIII B) and (XIII C) when treated with phosphorus oxychloride gave *iso*quinoline derivatives with the composition and structure corresponding to those of the O-methylpsychotrine alkaloid.[13]

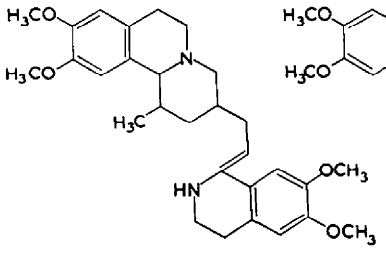
The bases of (XIV) were isolated as amorphous substances, m.p. 59–60° (XIV A), 58–59° (XIV B) and 58–59° (XIV C), unstable when exposed to atmospheric oxygen or sunlight. Their oxalates were isolated as readily crystalline hydrates with melting points coinciding, namely with (XIV A), 145·5–147° (dec.), with (XIV B), 146·5–148° (dec.), and with (XIV C), 145·5–147·5 (dec.). The (±)-tartrates crystallise as anhydrous compounds melting at 123–125° (XIV A), 125° (XIV B) and 160° (XIV C).

The N-acetyl-O-methylpsychotrines have also been prepared, their bases being isolated as colourless amorphous substances, m.p. 78–79° (XIV A), 98–99° (XIV B) and 73–74° (XIV C), and their oxalates, m.p. 147–148° (dec.) in the case of (XIV A), 152° (dec.) of (XIV B), and 151° (dec.) of (XIV C).

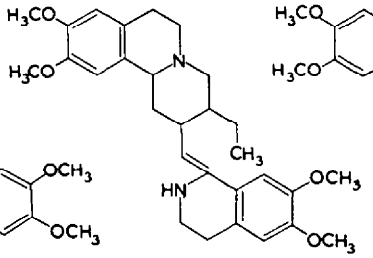
[13] R. P. Evstigneeva, R. G. Glushkov and N. A. Preobrazhensky, *Zh. Obshch. Khim.* XXVIII, 2463 (1958).

All bases, oxalates and (+)-tartrates of O-methylpsychotrines as well as the bases and oxalates of N-acetyl-O-methylpsychotrines show a depression of the mixed melting point.

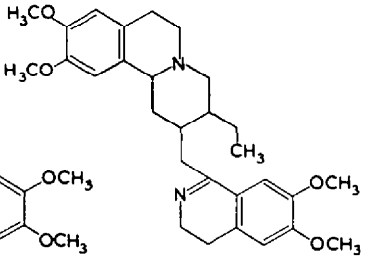
The ipecacuanha alkaloid O-methylpsychotrine was first discovered in 1917. It differs from emetine in having two hydrogen atoms less and can be obtained from the latter on oxidation with mercuric acetate. It was referred to as a secondary–tertiary base, since, when heated with benzoic anhydride, it gives a monosubstituted N-benzoyl derivative. In 1927, in accordance with one of the structures suggested for emetine, it had been assigned the following formula (XXVI):[14]



XXVI



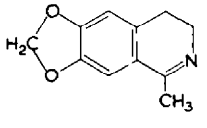
XXVII



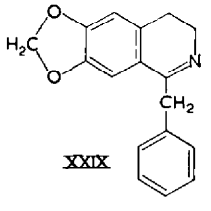
XIV

The position of the double bond was confirmed by the fact that the N-benzoyl-O-methylpsychotrine on oxidation with perphthalic acid and ozone yields N-benzoyl-corydaldine.[15]

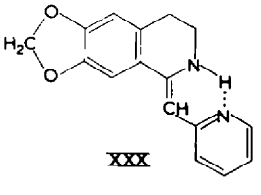
In 1949, on the basis of the structure of emetine, O-methylpsychotrine was assigned formula (XXVII), but more recent investigations of the ultra-violet absorption spectrum of O-methylpsychotrine have led to the conclusion about the double bond in the dihydro*iso*quinoline ring being in the 1:2-position (XIV).[16] This suggestion being, however, hardly compatible with the secondary–tertiary character of the base, the structure of O-methylpsychotrine still remained doubtful. The position of the double bond in the 3:4-dihydro*iso*quinoline ring was uncertain not only for O-methyl-psychotrine but for a whole group of similar compounds as well. Having studied the ultra-violet absorption spectra of 1-methyl-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (XXVIII), 1-benzyl-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (XXIX) and 1-(α-picolyl)-3:4 dihydro-6:7-methylenedioxy*iso*quinoline (XXX), and having compared them with those of stilbene and α-stilbazole, Bills *et al.*[17] suggested the exocyclic position of the double bond in (XXX) and the endocyclic one in (XXVIII) and (XXIX).



XXVIII



XXIX

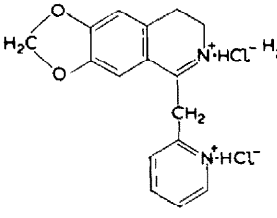


XXX

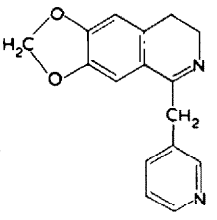
[14] W. H. Brindley and F. L. Pyman, *J. Chem. Soc.* 1067 (1927).
[15] P. Karrer, C. H. Eugster and O. Rüttner, *Helv. Chim. Acta* **31**, 1219 (1948).
[16] H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.* 391 (1952).
[17] J. L. Bills, C. R. Noller and M. Axima, *J. Amer. Chem. Soc.* **72**, 17 (1952).

During the conversion from base (XXX) to the hydrochloride (XXXI) the character of the absorption curve changes, apparently owing to the rearrangement of the double bond in the ring. The exocyclic structure of compound (XXX) seems to be accounted for by the possibility of the intramolecular hydrogen bond formation. This is confirmed by 1-(β-picolyl)-3:4-dihydro-6:7-methylendioxy*iso*quinoline (XXXII), which has no intramolecular hydrogen bond, having an endocyclic double bond, as shown by the absorption spectra and the conversion of (XXXII) into the *iso*quinoline derivative (XXXIII).

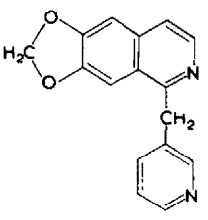
On the other hand, 1-(α-picolyl)-3:4-dihydro-6:7-methylenedioxy*iso*quinolien (XXX) gave no *iso*quinoline derivative.



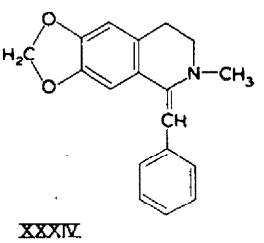
XXXI



XXXII



XXXIII



XXXIV

The investigations suggested that the position of the double bond for 1-substituted-3:4-dihydro*iso*quinoline compounds is endocyclic, and only in few cases is the exocyclic position possible.

Openshaw and Wood, comparing the ultra-violet data of the natural O-methylpsychotrine oxalate with those of 1-methyl-3:4-dihydro-6:7-methylenedioxy*iso*quinoline (XXVIII.HCl) came to the conclusion that the double bond in O-methylpsychotrine was endocyclic. Although this conclusion is ultimately correct, it cannot be arrived at solely in terms of the spectrum of the salt, since it is also necessary to have the spectral data concerning the base, as it is possible for the salt and the base to have a different position of the double bond.

We have therefore undertaken the spectral investigation of stereoisomeric synthetic O-methylpsychotrine oxalates. The ultra-violet absorption curves of the three isomers were found to coincide with and to be similar to that of the natural O-methylpsychotrine oxalate, which is also so for the spectra of (+)-O-methylpsychotrine tartrate.

We have also investigated the ultra-violet data concerning O-methylpsychotrine bases produced from purified oxalates. The absorption curves of the bases proved to be similar and their maxima situated similarly to those of the absorption curves of 1-methyl- and 1-benzyl-3:4-dihydro-6:7-methylenedioxyquinolines [(XXVIII) and (XXIX)]. Correspondingly, the structure of O-methylpsychotrine should be given by the formula (XIV) with an endocyclic bond.

It is known that O-methylpsychotrine yields monoacyl derivatives in which the double bond can be only exocyclic. N-Benzoyl- and N-succinyl-O-methylpsychotrines resulting from the natural O-methylpsychotrines are described in the literature. The N-acetyl derivatives of stereoisomeric O-methylpsychotrine have been obtained. The bases of N-acetyl-O-methylpsychotrines are more stable to light, the atmosphere and other influences. If O-methylpsychotrine is dissolved in carbon tetrachloride the solution becomes opaque, in 15–20 min, a red precipitate, m.p. 171–178° (164°), being produced. On the other hand, N-acetyl-O-methylpsychotrine base when dissolved in

carbon tetrachloride results in a clear solution, which remains unchanged for several days. The ultra-violet spectra of N-acetyl-O-methylpsychotrine bases and their oxalates proved respectively to be similar to those of O-methylpsychotrines, which is also so with 1-benzylidene-1:2:3:4-tetrahydro-2-methyl-6:7-methylenedioxy*iso*quinoline (XXXIV).

Ultra-violet data are thus not reliable enough to serve as a means of determining the position of the double bond.

Infra-red data provide in many cases better results. With O-methylpsychotrine the position of the double bond should be easily determined by making use of infra-red spectra as in the case of an exocyclic double bond present the molecule must involve the N—H group with a definite characteristic infra-red absorption band over the range 3500–3100 cm^{-1} (2·86–3·23 μ). The infra-red spectrum of the O-methylpsychotrine base (in petroleum jelly) shows no absorption bands at this frequency, thereby denoting the absence of the exocyclic double bond. The spectrum of the O-methylpsychotrine base in carbon tetrachloride also revealed the absence of the N—H group. The spectrum of a reference substance, dihomoveratrylamine, at the same concentration shows the band of the N—H group at 3293·5 cm^{-1}, indicating the presence of an intramolecular hydrogen bond. To investigate the hydrogen bond it is customary to substitute deuterium for hydrogen, and this often results in a sharp displacement of the characteristic frequency to a longer wavelength. We have attempted by this procedure to find the N—H group in O-methylpsychotrine. The deuterium–hydrogen exchange is known to proceed extremely readily in the alcoholic and amino groups,[18] whilst that of hydrogen linked with carbon does not take place at all under ordinary conditions.[19] The O-methylpsychotrine base was dissolved in dry dioxane and an excess of heavy water was added. After standing for 2 days the base was isolated and spectroscopically investigated. The N–D band has not been found, denoting the absence of an exocyclic bond in O-methylpsychotrine. With dihomoveratrylamine deuterium–hydrogen exchange did not take place. This is in accordance with other known facts of hindered hydrogen exchange when hydrogen is present in the intramolecular hydrogen bond. For example, hydrogen does not exchange in 1-hydroxyanthraquinone[20] or 1-benzeneazo-2-naphthylamine.[21] Thus the infra-red spectra of O-methylpsychotrine base indicated the presence of the endocyclic double bond. Spectroscopic investigation of O-methylpsychotrine was extremely complicated owing to the presence of water of crystallisation. On the basis of spectroscopic data in the 1200–1700 cm^{-1} region the absence of N–H group in the salt is definite.

The structure of O-methylpsychotrine therefore corresponds to formula (XIV). The formation of mono-N-acyl derivatives may be accounted for by tautomerism with a preferential shift to the compound with the endocyclic double bond (XIV).

The exocyclic position of the double bond (prototropic rearrangement) is due to the influence of alkali and is retained by the acylating agent.

The final step in the synthesis of emetine consists in the reduction of *O*-methylpsychotrine effected both catalytically and chemically. The reduction of the natural

[18] J. Hine and C. H. Thomas, *J. Amer. Chem. Soc.* **75**, 730 (1953); *Ibid.* **76**, 612 (1954); H. Kwart, L. P. Kuhn and E. L. Bannister, *J. Amer. Chem. Soc.* **76**, 5998 (1954).

[19] D. N. Kursanow, V. N. Setkina and A. P. Mestcher'akov, *Dokl. Akad. Nauk SSSR* **105**, 279 (1955); A. I. Shatenshtein, K. I. Zhdanova, L. I. Vinogradov and V. R. Kalinatchenko, *Dokl. Akad. Nauk SSSR* **102**, 779 (1955).

[20] D. N. Shigorin and N. S. Dokunikhin, *Dokl. Akad. Nauk SSSR* **100**, 323 (1955).

[21] G. D. Bagratishvilly, *Dokl. Akad. Nauk SSSR* **96**, 753 (1954).

O-methylpsychotrine with sodium in alcohol results in a mixture of emetine and *iso*-emetine. The catalytic hydrogenation is stereo-oriented.

Taking into consideration the main conformational positions available for emetine, it is possible to formulate eight most stable conformations and these correspond to the number of racemic isomers of the alkaloid in terms of the classical theory.

Four of these conformations have the rings B and C linked in the *trans* position and the other four in the *cis*-position. The large substituents are situated equatorially.

The carbon–carbon linkages at C_7 and C_1 are only equatorial, this being achieved by allowing for the conversion of ring D. The above conformational formulae of emetine seem to be the most plausible ones. The possibility of the existence of other isomeric forms must not be excluded, e.g., those with polar substituents at C_7 and C_1. The conformation of (−)-emetine (natural) should be expressed by one of the structures. In accordance with recent investigations[22] dealing with emetine stereochemistry, the natural alkaloid would be in α-conformation. This conclusion must however be considered as tentative, the absolute configuration at C_1 not having been determined.

In attempting to find suitable routes to synthesise (−)-emetine (natural), each of the isomeric O-methylpsychotrines was reduced with hydrogen under three different conditions: (a) in the presence of platinic oxide in acidic medium, (b) in the presence of platinic oxide in ammonia–alkali medium and (c) with Raney nickel in neutral medium.

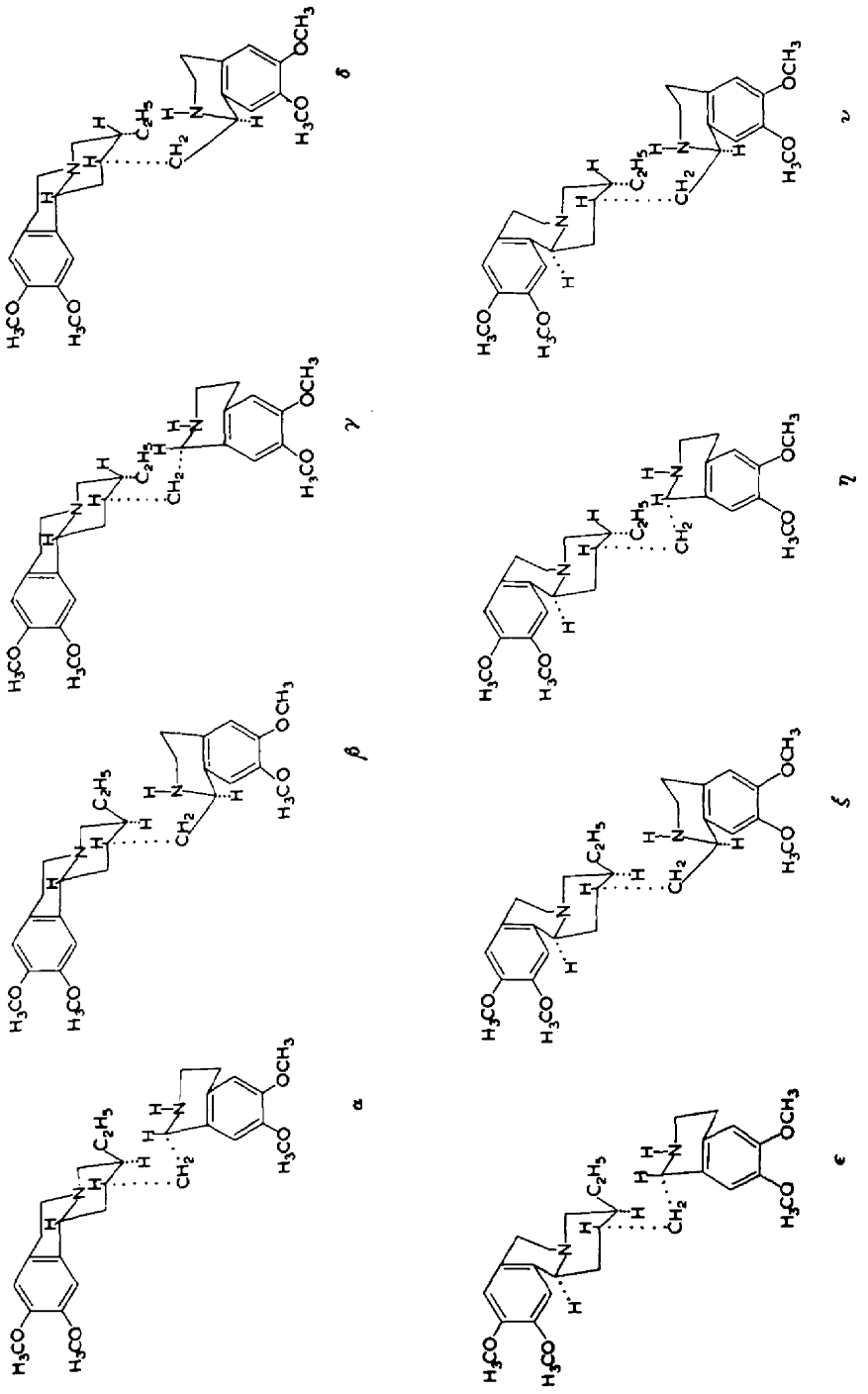
For convenience each emetine is designated by two signs, the first denoting the conditions of the hydrogenation of the quaternary chloride of the quinolizine derivative of (XI), the second one characterising conditions of the hydrogenation of the 3:4-dihydro*iso*quinoline nucleus of O-methylpsychotrine. We have thus obtained eight isomeric substances: 1, AB; 2, AA; 3, AC; 4, BB; 5, BA; 6, BC; 7, CC and CB; 8, CA.

Emetine has also been produced via a shortened synthetic route (B) through the diamide (XV) with a simultaneous closure of two *iso*quinoline rings (XVI) and hydrogenation of two double bonds (III) in the presence of Raney nickel.

Hydrogenation of O-methylpsychotrines proceeds in all cases in nearly quantitative yield, the bases being isolated as oily or amorphous substances. Anhydrous hydrates are also amorphous, readily absorb moisture in the air and give crystalline hydrates which are not suitable for comparing isomeric compounds, as they lack sharp melting points and anhydrous salts of emetine are very hydroscopic, the drying of emetine being rather difficult because it is often accompanied by change in the substance. Crystalline salts of (−)-emetine with mineral acids described in the literature appear only as hydrates. We have obtained a number of salts of (−)-emetine with organic acids, the most striking being the camphor-β-sulphonates, which readily crystallise without hydrate formation.

The (+)-camphor-β-sulphonate of (−)-emetine was investigated as regards infra-red spectra. For comparison the infra-red spectra of the (−)-emetine base and (±)-camphor-β-sulphonic acid were taken, the former distinctly revealing the absorption band of the non-associated N–H group at 3371 cm^{-1}. The spectrum of (−)-emetine

[22] A. R. Battersby, R. Binks, D. Davidson, G. C. Davidson and T. P. Edwards, *Chem. & Ind.* 982 (1957); A. R. Battersby and S. Cox, *Chem. & Ind.* 983 (1957); E. van Tamelen, P. E. Aldrich and J. B. Hester, *J. Amer. Chem. Soc.* **79**, 4817 (1957).


α
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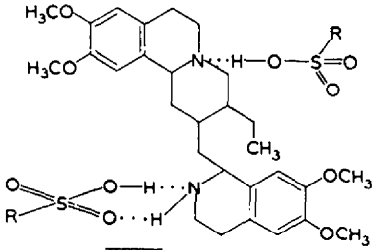
(±)-camphor-β-sulphonate shows three new bands that can be referred to salt formation (2512, 2556 and 2600 cm^{-1}). On comparing it with the infra-red absorption-spectra of (±)-camphor-β-sulphonates of aniline, pyridine and piperidine, (−)-emetine (±)-camphor-β-sulphonate was found to represent a complex compound involving one molecule of the base and two of (±)-camphor-β-sulphonic acid linked with hydrogen.



XXXV

The (+), (−) and (±)-camphor-β-sulphonic acids were used to obtain salts for the investigation of synthetic isomeric emetines.

The reaction of emetine bases with (+)-, (−)- and (±)-camphor-β-sulphonic acids in alcoholic solution gives crystalline salts. Isomeric camphor-β-sulphonates are very similar as regards melting points, but differ in solubility in ethanol. Their mixed melting points all show a depression, except those of the respective camphor-β-sulphonates CC and CB. The ultra-violet spectra of (±)-camphor-β-sulphonates are similar with the same maxima (235 mμ and 285 mμ) and minimum (255 mμ), but slightly different in the intensity of the first maximum and minimum. The emetine bases derived from crystalline camphor-β-sulphonates have very similar melting points, that is: 1, 74–75° (60°); 2, 71·5–72° (68°); 3, 72·5–73° (67°); 4, 70–71° (66·5°); 5, 68–70° (65°); 6, 74–75° (65°); 7, 73·5–74·5° (70°); 8, 95–96° (73°); but they show a depression of their mixed melting points. For example, the mixture of emetine bases 7, CB, and 8, CA, melts at 50° with deformation, softens at 59° and forms a meniscus at 84°. Difficulty is experienced in determining the mixed melting points, since the emetine bases are more readily electrified than the camphor-β-sulphonates when ground. After the separation of crystalline (+)-camphor-β-sulphonates about 50 per cent of salt remains in the alcoholic mother-liquor and is not precipitated even after prolonged standing in the cold, and other solvents also proved to have little effect, and the free bases were isolated to obtain oxalates. The latter contain water of crystallisation (about 1 molecule) and melt at: 1, 166° (152°); 2, 167–168° (156°); 3, 166° (157°); 4, 154° (148°); 5, 158° (140°); 6, 166° (161°); 7, 166–167° (156°); 8, 177–178° (156°); their ultra-violet spectra are also nearly similar. The oxalates yielded bases melting at: 1, 73–74° (60°); 2, 71–71·5° (68°); 3, 72·5–73° (65°); 4, 70–71° (65°); 5, 68–70° (65°); 6, 74–75° (65°); 7, 73·5–74·5° (70°); 8, 95–96° (73°); their properties were similar to those of the natural alkaloid. The melting points, ultra-violet spectra and rotation of the base and oxalate of isomer CC proved to be identical with those of the natural alkaloid. Several (−)-emetine salts have been obtained, namely, (+)-camphor-β-sulphonate of emetine, $C_{29}H_{40}O_4N_2.2C_{10}H_{16}O_4S$, m.p. 229–231·5°, $[\alpha]_D^{20°}0°$(*c*, 7·46 in water), isolated from alcohol as fine plates or needles; (+)-camphor-β-sulphonate of (−)-emetine, $C_{29}H_{40}O_4N_2.2C_{10}H_{16}O_4S$, m.p.

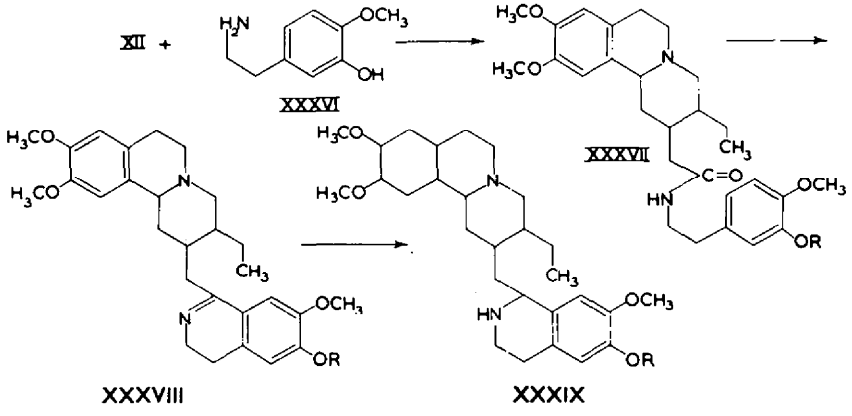
215° (212°), $[\alpha]_D^{20°}$ + 13·85° (*c*, 8·77 in water), isolated from acetone as fine plates; (−)-camphor-β-sulphonate of (−)-emetine, $C_{29}H_{40}O_4N_2.2C_{10}H_{16}O_4S$, m.p. 235·8–236·5° (223°), $[\alpha]_D^{15·5°}$ −8·4° (*c*, 8·43 in water), isolated from water as long tetragonal prisms; (+)-tartrate of (−)-emetine $C_{29}H_{40}O_4N_2.2C_4H_6O_6$, m.p. 159–161·5°, 170° (dec.), $[\alpha]_D^{15·5°}$ + 16·2° (*c*, 7·29 in water), isolated from alcohol as an amorphous substance; (−)-tartrate of (−)-emetine, $C_{29}H_{40}N_2O_4.2C_4H_6O_6.\frac{1}{2}H_2O$, m.p. 155° and 172° (dec.), $[\alpha]_D^{13·5°}$ 0°(*c*, 5·14 in water), isolated from alcohol as an amorphous substance.

Oxidation of the synthetic base of (−)-emetine with iodine resulted in rubremetinium iodide similar in properties to that produced from the natural alkaloid.

Synthesis of phenolic bases of ipecacuanha alkaloids of psychotrine and cephaeline

The phenolic bases of ipecacuanha (+)-psychotrine and (−)-cephaeline are derived from the plant in minute quantities and are very difficult to purify.

The syntheses of (±)-psychotrine (XXXVIII; R = H), (±)-cephaeline (XXXIX; R = H) and their derivatives have been effected following the scheme elaborated for emetine:



The methyl 4′:5′-dimethoxy-6-ethyl-3:4:5:6:7:8-hexahydrobenzo-(1:2:1′:2′)-quinolizyl-7-acetate (XII; R = CH_3) was obtained following the procedure described above, with Raney nickel to reduce the quaternary chloride. The melting temperature of the hydrochloride (crystalline hydrate) was 195–195·5°. β-(3-Hydroxy-4-methoxyphenyl)ethylamine was obtained selectively by demethylating homoveratrylamine with metallic sodium in liquid ammonia,[23] m.p. 147–148°; the hydrochloride melted at 204–206°. Condensation of (XII) with β-(3-hydroxy-4-methoxyphenyl)ethylamine (XXXVI) resulted in the hydroxyamide (XXXVII, R = H), m.p. 101–102°. By reaction with benzyl chloride this hydroxyamide gave the corresponding O-benzyl derivative (R = $CH_2C_6H_5$), m.p. 106–107°, which on being cyclised with phosphorus oxychloride gave O-benzylpsychotrine (XXXVIII), R = $CH_2C_6H_5$). The base was isolated as an amorphous yellow substance, m.p. 142–146°; the hydrochloride melted at 204–207°.

O-Benzylpsychotrine was reduced in the presence of platinic oxide to O-benzylcephaeline (XXXIX, R = $CH_2C_6H_5$), the base melting at 137–140°.

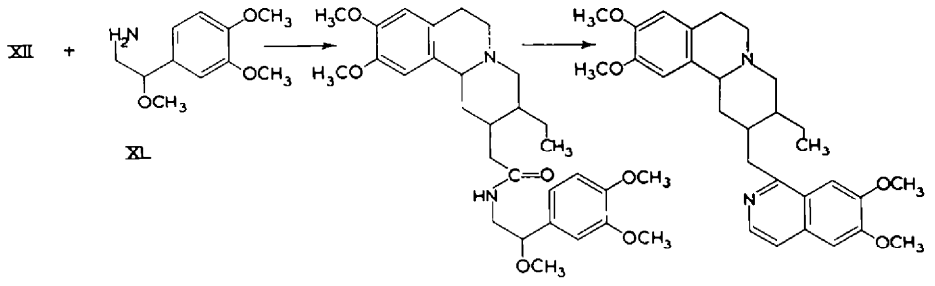
[23] K. E. Hamlin and F. E. Fischer, *J. Amer. Chem. Soc.* 75, 5119 (1953).

The ultra-violet absorption spectra of the intermediates were similar to those of the intermediates in the synthesis of emetine.

Synthesis of emetamine

Emetamine differs from emetine in having four hydrogen atoms less. It was suggested in 1827 that the emetamine structure involves an *iso*quinoline ring whilst emetine is a derivative of tetrahydro*iso*quinoline. When the structure of emetine had been established, emetamine was assigned formula (XLII). Recently this structure has been confirmed by the investigation of the oxidation products of the bisbenzyl chlorides of emetamine and of O-methylpsychotrine.[24]

Following the scheme worked out for emetine, we carried out the synthesis[25] by condensation of the methyl ether (XII; R = CH_3) with β-(3:4-dimethoxyphenyl)-β-methoxyethylamine[26] (XL), as follows:



Heating ester (XII; R = CH_3) with (XL) gave the amide (XLI), isolated from ethanol as colourless crystals, m.p. 172·5–173·5°. Cyclisation of the amide with phosphorus oxychloride gave emetamine, m.p. 124–125°, and the oxalate, m.p. 141·5–142·5°. Oxidation of the (±)-base of emetamine with bromine resulted in rubremetamine bromide, obtained as orange-red crystals, m.p. 170–185°. The ultra-violet absorption spectrum of the synthetic rubremetamine bromide was found to be identical with that of the rubremetamine bromide produced from the natural alkaloid.

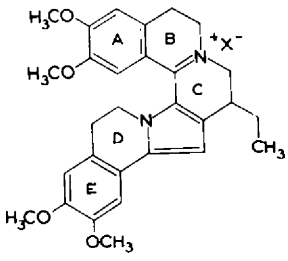
Synthesis of emetine analogues

One of the most interesting features in the chemistry of alkaloids of ipecacuanha is the oxidation of (—)-emetine with mild oxidising agents such as ferric chloride, bromine, iodine and mercuric acetate. The red compound isolated and referred to as dehydroemetine or rubremetine, $C_{23}H_{33}O_4N_2$, contains seven hydrogen atoms fewer than emetine. The formation of rubremetine is accompanied by structural changes, one of the nitrogen atoms losing its basicity and the second one becoming quaternary. Until recently the structure of rubremetine remained ambiguous until Openshaw succeeded in proving that its structure corresponded to (XLIII).[27]

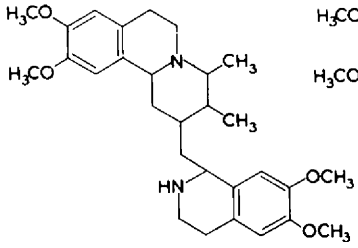
Formula (XLIII) accounts for all the chemical properties of this compound, including the fact that the oxidation of N-methylemetine cannot result in a substance

[24] A. R. Battersby, *Chemical Society Special Publication* No. 3, p. 36. London (1955).
[25] R. P. Evstigneeva, J. Braier and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR* **117**, 227 (1957).
[26] M. G. Tsatsas, *Bull. Soc. Chim. Fr.* **16**, 884 (1949).
[27] H. T. Openshaw, *Chemical Society Special Publication* No. 3, p. 28. London (1955).

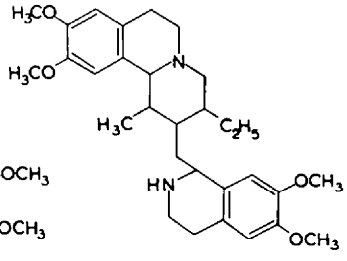
similar to rubremetine. In order to show the effect of substituents in the ring C on the formation of the red compound, the synthesis of two emetine analogues with alkyl substituents in two free positions at C_5 and C_6 was undertaken, namely 4′:5′-dimethoxy-:65-dimethyl-7-(1″-methyl-6″:7″-dimethoxy-1″:2″:3″:4″-tetrahydro-*iso*quinolyl)-3:4:5:6:7:8-hexahydrobenzo-1:2:1′:2′-quinolizine[28] (IV), and 8-methyl-emetine[29] (XLIV).



XLIII

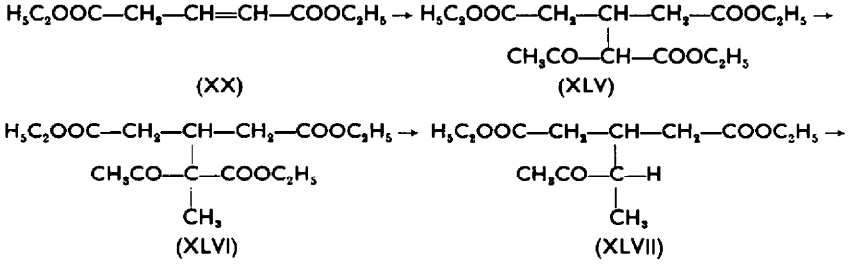


IV

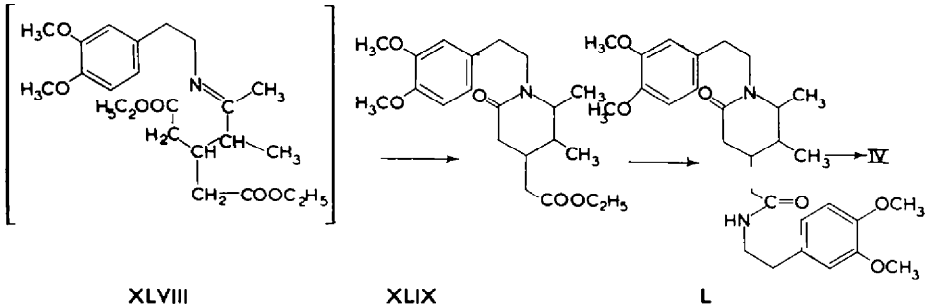


XLIV

The synthesis of (IV) was effected by starting with ethyl glutaconate, according to the scheme:



(XX) (XLV) (XLVI) (XLVII)



XLVIII XLIX L

By condensing ethyl glutaconate and acetoacetate ethyl β-(acetocarbethoxy) methylglutarate (XLV), b.p. 167–169°/2·5–3 mm, was obtained. On treatment with methyl halide it was converted into ethyl β-(α'-aceto-α' carbethoxy)ethylglutarate (XLVI), b.p. 149–151°/1·4 mm. The latter was saponified with sodium ethoxide and water to yield after decarboxylation ethyl β-(α'-aceto)ethylglutarate (XLVII), b.p. 110–112°/1 mm. This ester reacted readily with 1 mole of homoveratrylamine to

[28] R. P. Evstigneeva, N. M. Kashnikova, M. S. Bainova and N. A. Preobrazhensky, *Zh. Obschh. Khim.* XXVIII, 1184 (1958).

[29] R. P. Evstigneeva, L. V. Lavrova, C. D. Zarankina and N. A. Preobrazhensky, *Zh. Obshch. Khim.* XXVIII, 1190 (1958).

form the Schiff's base (XLVIII), which was hydrogenated in the presence of platinic oxide. The reduction product was cyclised to the corresponding piperidone derivative (XLIX) by heating on a water-bath *in vacuo*. The resulting substance was condensed with a second molecule of homoveratrylamine by heating at 180°. The diamide (L), after cyclisation with phosphorus oxychloride and reduction of the quaternary chloride, yielded 4′:5′:-dimethoxy-5:6-dimethyl-7-(1″-methyl-6″:7″-dimethoxy-1″:2″:3″:4″-tetrahydro*iso*quinolyl)-3:4:5:6:7:8-hexahydrobenzo-1:2:1′:2′-quinolizine (IV) as a thick yellow oil, the melting point of the hydrochloride being 134–135°.

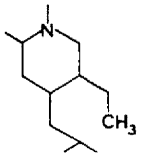
The synthesis of 8-methylemetine XLIV has been effected starting with ethyl acetonedicarboxylate, which was methylated by methyl halides to give ethyl α-methyl-acetonedicarboxylate, b.p. 118–119°/2 mm. The subsequent procedure was similar to that for emetine, requiring the preparation of the following: ethyl α-methyl-glutaconate, b.p. 104–105°/2 mm; ethyl α-methyl-β-cyano-β-carbethoxymethyl-glutarate, b.p. 155–156°/1 mm; ethyl α-methyl-β-(α′-cyano-α′-carbethoxy)propyl-glutarate, b.p. 158–159°/1 mm; ethyl α-methyl-β-(α′-cyano)propylglutarate, b.p. 130–132°/1 mm. The anhydrous ethyl chloride of the quinolizine derivative was isolated as an amorphous substance, m.p. 126–127°, the crystalline hydrate melting at 184–185·5°, and 8-methylemetine was produced as a yellow oil, the hydrochloride melting at 121–122°.

The bases of the emetine dimethyl analogue (IV) and 8-methylemetine (XLIV) were oxidised with bromine, the former giving an orange-red substance, m.p. 164–180°, whose ultra-violet spectrum was identical with that of rubremetine, the latter yielding a yellow substance, m.p. 195–198°, but, when oxidised with iodine, an amorphous yellow substance, m.p. 135–140°, is obtained, both substances being markedly different in their properties from rubremetine.

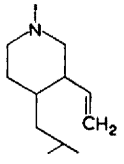
It follows that the alkyl substituent at C_8 hinders the formation of the red compound, thus confirming the participation of hydrogen atoms at C_8 in rubremetine formation from emetine.

Close relationship of iso*quinoline, quinoline and indole synthesis*

The results obtained from the synthetic investigation of the alkaloids of ipecacuanha enable us to turn to the syntheses of other substances involving a piperidine group similar to that (B) in emetine (A) such as meroquinene, homomeroquinene (B) and their dihydro derivatives.



A

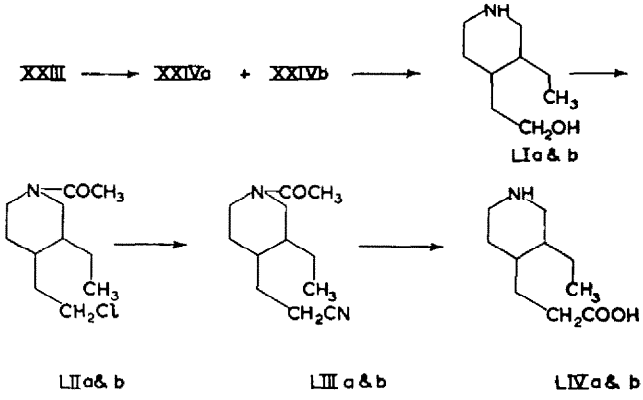


B

It has been shown that the use of the same starting compounds leads through a similar conversion to the synthesis of alkaloids of ipecacuanha and the cinchona bark alkaloids.[30]

[30] N. A. Preobrazhensky, R. P. Evstigneeva, G. S. Levtchenko and Fed'ushkina, *Dokl. Akad. Nauk SSSR* **81**, 421 (1951).

The scheme worked out required homocincholoipon and homomeroquinene. The synthesis of *cis*-homocincholoipon to obtain dihydroquinine was carried out with ethyl δ-ethyl-α-piperidone-γ-acetate (XXIV). The synthesis of the isomeric *cis*- and *trans*-homocincholoipons was also effected by starting with diethyl β-(α'-cyano) propylglutarate, the principal intermediate in the synthesis of ipecacuanha alkaloids, according to the following scheme.[31]



Hydrogenation of ethyl β-(α'-cyano)propylglutarate (XXIII; $R = C_2H_5$) gave 4-carboethoxymethyl-5-ethylpiperidone-2, isolated in two isomeric forms: (1) a crystalline substance (XXIVa), m.p. 84–85°, very sparingly soluble in ether and (2) an oily substance (XXIVb), b.p. 175–176°/1·5 mm, readily soluble in ether. Subsequently, both isomers were synthesised separately. The reduction of 4-carbo-ethoxymethyl-5-ethylpiperidones with lithium aluminium hydride gave 3-ethyl-4-(β-hydroxyethyl) piperidines (LIa and LIb), b.p. 131–132°/3 mm and 127–128°/2·5 mm, respectively. The treatment of the 3-ethyl-4-(β-hydroxyethyl)piperidine hydrochlorides with thionyl chloride gave 3-ethyl-4-(β-chloroethyl)piperidine hydrochlorides, which, without being isolated, were converted into N-acetyl-3-ethyl-4-(β-chloroethyl) piperidines (LIIIa and LIIIb), b.p. 156–157°/2 mm and 157–158°/2 mm, respectively. Treatment of these substances with potassium cyanide gave N-acetyl-3-ethyl-4-(β-cyanoethyl)piperidine, b.p. 165–168°/3 mm (LIIIa) and 168–172°/3 mm (LIIIb), which, on saponification gave 3-ethyl-4-(β-carboxyethyl)piperidines, or homocincholoipons (LIVa and LIVb).

The crystalline and oily isomeric forms of 4-carboethoxymethyl-5-ethylpiperidone-2 gave aurichlorides (homocincholoiponic aurichlorides) melting, respectively, at 174·4–175° and 194·5–195° and mixed melting point 155–151°.

The structural determination of the homocincholoipons was carried out by comparing the intermediates of homocincholoipon synthesis (LIa) and LIb with 3-ethyl-4 (β-hydroxyethyl)piperidine (LIc) produced from natural quinine via meroquinene, the piperidine products of quinine decomposition being known to retain the *cis*-configuration. The meroquinene ethyl ester was reduced with lithium aluminium hydride to 3-vinyl-4-(β-hydroxyethyl)piperidine.

The latter was hydrogenated in the presence of platinic oxide to give 3-ethyl-4-β-hydroxyethyl)piperidine (LIc), b.p. 115–116°/1·5 mm. The infra-red spectra of

[31] J. F. Malina, R. P. Evstigneeva and N. A. Preobrazhensky, *Chem. and Chem. Technol.* In press (1957).

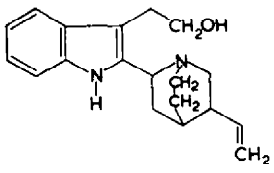
(LIa), (LIb) and (LIc) have substantiated the identity of our synthetic compounds with those obtained from the natural quinine. The spectrum of (LIb) produced from the oily 4-carboethoxymethyl-5-ethylpiperidone (XXIVb) differs from those of (LIa) and (LIc) in the 1290 cm^{-1} and 700–750 cm^{-1} range.

This data suggests that both the crystalline 4-carboethoxymethyl-5-ethylpiperidone-2 and the homocincholoipon synthetically obtained from it (LIVa) are *cis*, while the oily 4-carboethoxymethyl-3-ethylpiperidone-2 (XXIVb) and the homocincholoipon (LIVb) are *trans*.

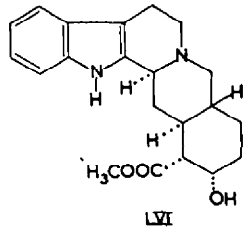
The synthetic routes of ipecacuanha alkaloids and those of the cinchona bark are thus very similar, the close relationship between these two alkaloids being also indicated by the theory of biogenesis.[32]

The alkaloids of cinchona bark are divided into two large groups, first, the quinoline derivatives such as quinine, quinidine, and cinchonine, and, secondly, the indole derivatives such as cinchonamine and quinamine. The syntheses of the major alkaloids of the quinoline series including that of quinine itself have already been effected, but the synthetic study of the quinine alkaloids of indole structure is far from being complete, although these substances are of great theoretical interest as being biogenetically and structurally related to such physiologically valuable organic compounds as yohimbine, reserpine (serpasil) and so on.

We have succeeded in finding synthetical routes for the quinine alkaloid of the indole group, cinchonamine (LV)[33] as a bridge between the quinine alkaloids of the quinoline series and the alkaloids of the indole series and have also effected the synthesis of yohimbine (LVI)[34]:



LV



LVI

These investigations are, however, beyond the scope of the present paper and will be reported later.

[32] R. Woodward, *Angew. Chem.* **68**, 13 (1956).
[33] Tcheng Tchang-by, R. P. Evstigneeva and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR*. In press (1958)
[34] L. A. Axanova and N. A. Preobrazhensky, *Dokl. Akad. Nauk SSSR* **117**, 81 (1957).