707. *Ipecacuanha Alkaloids. Part IV.* The Relative and Absolute Stereochemistry of the Benzoquinolizidine System of Emetine.*

By A. R. Battersby and S. Garratt (née Cox).

Protoemetine (II; R = CHO), which is known to have the same stereochemistry as emetine, has been reduced to deoxyprotoemetine (II; R = Me). The two possible diastereoisomers of (II; R = Me) having the ethyl groups respectively *cis* and *trans* have been synthesised stereospecifically. By comparison of these products with deoxyprotoemetine, the latter has been proved to be the *trans*-base. Thus protoemetine has the stereochemistry (V) and it follows that emetine has the structure (XXII; R = Me). This leads to a knowledge of the stereochemistry of the minor alkaloids of Ipecacuanha.

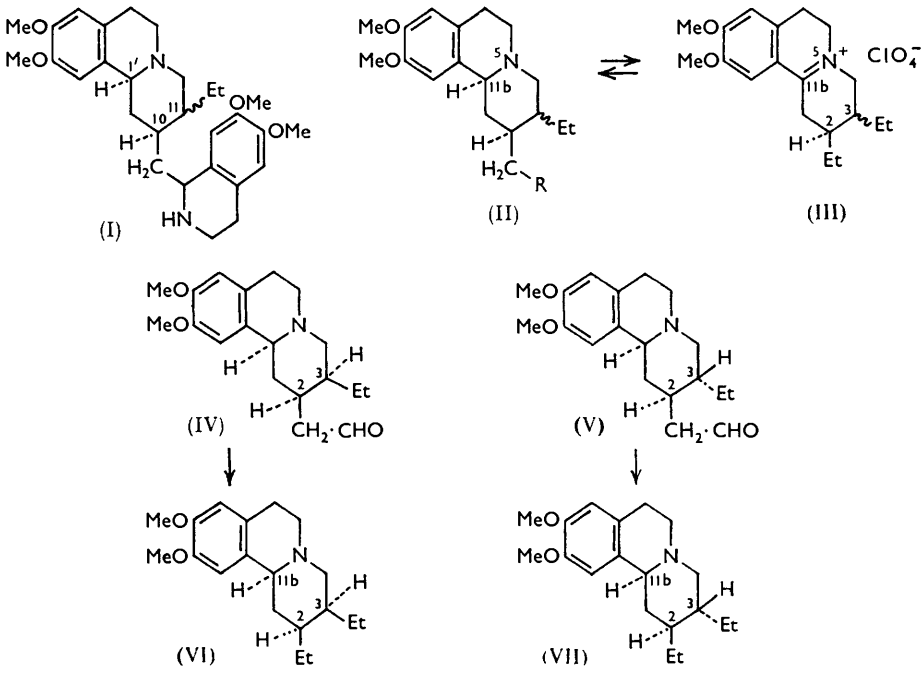
In Part III,* it was established that the tricyclic system of emetine (I) has the stereochemistry shown or that it has the mirror image form of this structure. Recently we have proved [1] that the *absolute* stereochemistry drawn for emetine (I) is in fact the true one; thus, only the relative configuration of the 11-ethyl group remains to be determined. The present paper describes the use of protoemetine (II; R = CHO), the aldehydic Ipecacuanha alkaloid,[2] to provide a solution to this problem. Protoemetine is an ideal starting point

* Part III, *J.*, 1959, 2704.

[1] Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86.

[2] Battersby, Davidson, and Harper, *J.*, 1959, 1744.

since Battersby and Harper have converted it into emetine;[3] the two alkaloids therefore have the same relative and absolute stereochemistry. It follows that protoemetine must have the structure (IV) or (V) depending upon whether there is a *cis*- or a *trans*-arrangement, respectively, about the 2,3-bond corresponding to the 10,11-bond of emetine. A decision



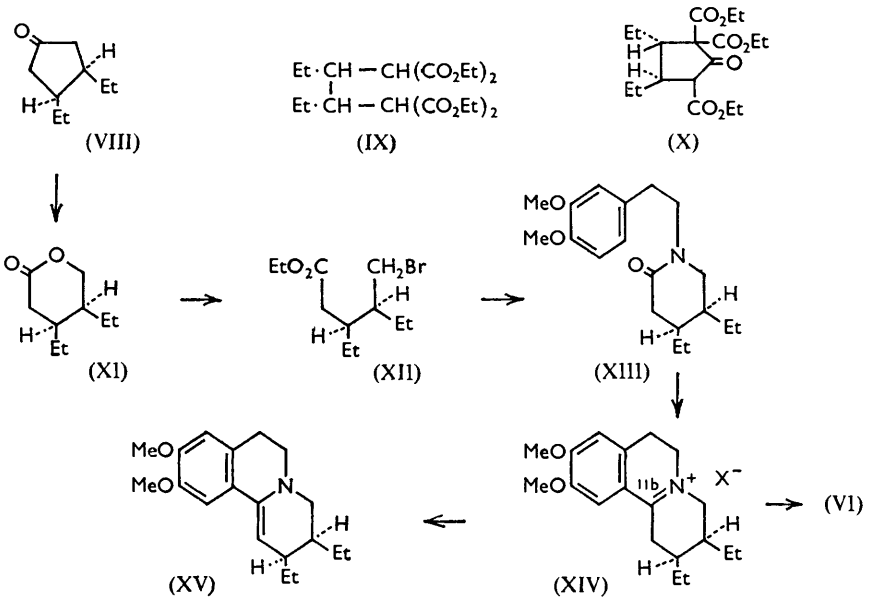
between the two possibilities was reached by reduction of protoemetine to deoxyprotoemetine which must have the structure (VI) or (VII); stereospecific syntheses of these two bases then provided the necessary materials for comparison with deoxyprotoemetine. For simplicity, only one enantiomer of each synthetic product is drawn in this paper, although the products are in fact all racemic.

Clemmensen reduction of protoemetine (II; R = CHO) gave a mixture from which only dihydroprotoemetine (II; R = CH_2·OH) could be isolated; we therefore turned to Wolff–Kishner reduction (Huang-Minlon modification [4]). Gates and Tschudi [5] found in one case that this modification can be used successfully at much lower temperatures than those (~200°) originally suggested, and Barton, Ives, and Thomas [6] showed that the reducing power is greatly improved when all the components in the reaction mixture are completely anhydrous. Combining these observations, we reduced protoemetine semicarbazone at 155° in anhydrous ethylene glycol with anhydrous hydrazine and alkali. Deoxyprotoemetine (II; R = Me) was isolated in 87% yield as its crystalline perchlorate.

The possibility that base-catalysed inversion of one or more asymmetric centres could have occurred in the above reduction was eliminated by subjecting emetine (I) to the Wolff–Kishner conditions. It was found that 94% of the non-phenolic basic material isolated from this reaction was unchanged emetine and the identity of the recovered alkaloid was established by rigorous comparison with the natural base and by conversion into the crystalline *N*-benzoylemetine. There is thus no doubt that deoxyprotoemetine (II; R = Me), which expanded becomes structure (VI) or (VII), has the same stereochemistry as protoemetine and emetine.

[3] Battersby and Harper, *J.*, 1959, 1748.
[4] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[5] Gates and Tschudi, *ibid.*, 1956, **78**, 1380.
[6] Barton, Ives, and Thomas, *J.*, 1955, 2056.

Dehydrogenation of deoxyprotoemetine (II; R = Me) with mercuric acetate [7] gave dehydrodeoxyprotoemetine perchlorate (III) which had the expected ultraviolet absorption. Catalytic hydrogenation of this salt gave the starting material (II; R = Me) in high yield; hydrogen is therefore added at position 11b *cis* with respect to the 2-hydrogen atom.



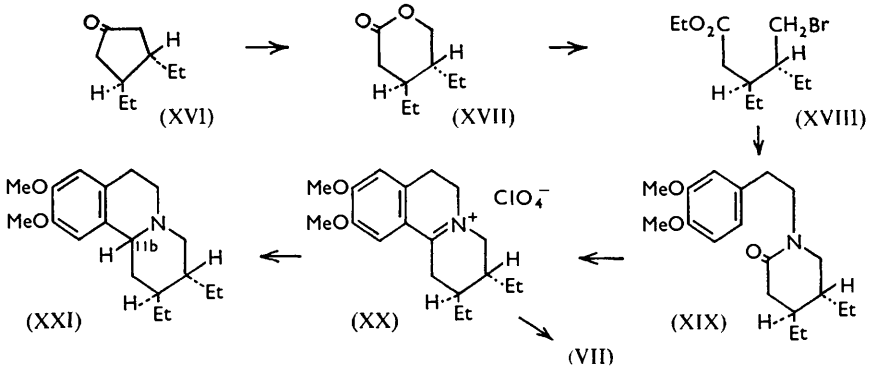
This observation was of considerable importance in plans for a stereospecific synthesis of emetine [8] and it is discussed further below.

The synthetic route to the diethyl bases (VI) and (VII) was suggested by that used for the controlled synthesis of alloyohimbane [9] and yohimbane [10] and it will be illustrated for the synthesis of the *cis*-base (VI). *cis*-3,4-Diethylcyclopentanone (VIII) had been prepared by Koelsch and Stratton [11] who firmly established its stereochemistry. We followed their method which has an interest aside from our main theme since it involves at one stage the treatment of a mixture of (±)- and *meso*-diethyl αδ-diethoxycarbonyl-βγ-diethyladipate (IX) under weakly basic conditions. The resultant formation of triethyl 4,5-diethyl-2-oxocyclopentane-1,1,3-tricarboxylate (X) from the (±)-ester whereas the *meso*-ester is largely unchanged can now be interpreted as conformational control of the 1,2-*cis*-cyclisation; [12] one can compare the case of acetone condensing at a slower rate with *meso*- than with (±)-dihydrobenzoin.[13]

The action of perbenzoic acid on the *cis*-diethylcyclopentanone (VIII) yielded the lactone (XI) of *erythro*-βγ-diethyl-δ-hydroxyvaleric acid which was converted into ethyl *erythro*-δ-bromo-βγ-diethylvalerate (XII) by hydrogen bromide in ethanol. Simple distillation did not separate the bromo-ester (XII) from unchanged lactone, but the bromine content of our product showed that it contained about 80% of the required bromide. This reacted readily with 3,4-dimethoxyphenethylamine in the presence of potassium carbonate to give the 2-piperidone (XIII); the structure is assigned on the basis of the analysis of this neutral product and of its infrared spectrum which showed a strong band at 1640 cm.$^{-1}$ (N·CO), but no OH or NH bands. The piperidone was cyclised by

[7] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[8] Battersby and Turner, *Chem. and Ind.*, 1958, 1324.
[9] Stork and Hill, *J. Amer. Chem. Soc.*, 1954, **76**, 949.
[10] van Tamelen and Shamma, *ibid.*, p. 950.
[11] Koelsch and Stratton, *ibid.*, 1944, **66**, 1881.
[12] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[13] Hermans, *Z. phys. Chem.*, 1924, **113**, 337.

phosphorus oxychloride in boiling toluene, and the product was isolated as the crystalline iodide (XIV; $X^- = I^-$) or perchlorate (XIV; $X^- = ClO_4^-$). The latter salt showed the ultraviolet spectrum characteristic of 3,4-dihydroisoquinolinium quaternary salts and the spectrum was altered in the expected way on addition of alkali owing to the formation of the anhydro-base (XV).



It has been well established by Linstead and his co-workers [14] that hydrogen is transferred from a catalyst to the least hindered side of an unsaturated molecule. We can therefore assign the structure (VI), which is the required (±)-*cis*-diethyl base, to the product formed in 74% yield by catalytic hydrogenation of the perchlorate (XIV; $X^- = ClO_4^-$). Reduction of the latter salt with sodium borohydride also gave the same base (VI).

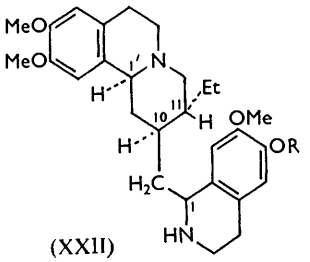
For the synthesis of the corresponding (±)-*trans*-diethyl base (VII), *trans*-3,4-diethylcyclopentanone (XVI) was regenerated by acid hydrolysis from its pure semicarbazone which is readily available by Koelsch and Stratton's method.[11] The remaining stages to the quaternary salt (XX), as shown in the charts, follow those used in the *cis*-series; the *threo*-bromo-ester (XVIII) has recently been prepared independently [15] for closely related studies in the indole series. In contrast to the *cis*-isomer (XIV), the two sides of the *trans*-molecule (XX) are about equally open to approach by the catalyst, so that one cannot predict the result of catalytic hydrogenation on steric grounds. In practice, the hydrogenation and also reduction with sodium borohydride gave the same isomer in good yield, and the infrared spectrum of this product, determined in solution, was identical with that of the reduction product from protoemetine known to have the structure (VI) or (VII). The infrared spectrum of the (±)*cis*-base (VI) was clearly different from that of the *trans*-isomer. These results establish conclusively that the reduction product from protoemetine is the *trans*-base (VII); it follows that protoemetine has the structure (V) and emetine the structure (XXII; R = Me).

Further support was obtained by showing that the infrared spectrum of the salt (III), obtained by mercuric acetate dehydrogenation of deoxyprotoemetine (II; R = Me), was identical with that of the synthetic *trans*-salt (XX); both spectra were determined in solution. The spectrum given by the synthetic *cis*-salt (XIV; $X = ClO_4^-$) was significantly different. These results also establish the illustrated position of the double bond in the salt (III) which we assigned above on the basis of ultraviolet absorption.

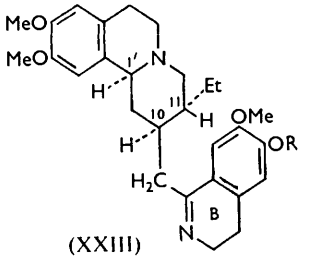
The foregoing evidence shows that hydrogenation of the *trans*-salt (XX) yields the more thermodynamically stable base (VII) rather than the other possible product (XXI). This also occurs when indole derivatives closely related to our materials are hydrogenated; thus 3-dehydroyohimbane chloride yields mainly yohimbane [10] and there are other similar cases.[15,16] It seems probable that thermodynamic control is a general phenomenon for this type of hydrogenation.

[14] Davis, Doering, Levine, and Linstead, *J.*, 1950, **1423**; Linstead and Whetstone, *ibid.*, p. 1428 and refs. therein.
[15] van Tamelen, Aldrich, and Katz, *J. Amer. Chem. Soc.*, 1957, **79**, 6426.
[16] Wenkert and Roychaudhuri, *J. Org. Chem.*, 1956, **21**, 1315.

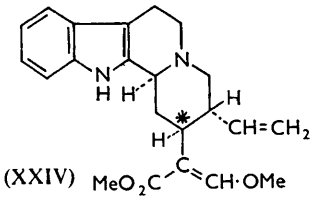
Reduction of the *trans*-salt (XX) by zinc in acetic acid gave the base (VII) together with an isomeric base which was separated as the sparingly soluble picrate. The latter base was shown to be tertiary by its failure to react with acetic anhydride and it was dehydrogenated by mercuric acetate in acetic acid with regeneration of the starting material (XX); the new isomer must therefore have the structure and stereochemistry (XXI). There was a clear difference between the infrared spectra of the bases (VII) and



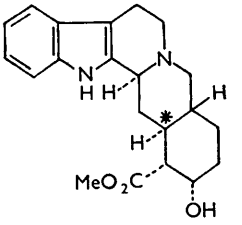
(XXII)



(XXIII)



(XXIV)



(XXV)

(XXI) when examined as films, and both showed the absorption at 2750 ± 10 cm.$^{-1}$ characteristic of the *trans*-conformation of the quinolizidine system.[17] In this conformation the base (XXI) has two axial ethyl groups and attempts were made to convert it into the thermodynamically more stable base (VII) by using potassium t-butoxide in boiling t-butyl alcohol for 20 hr. These conditions did not cause fission of the weakly activated $C_{(11b)}$–H bond which is necessary for the desired conversion, and the starting material was recovered unchanged; similarly the base (VII) was unaffected under these conditions. More drastic treatment of the bases for 13 hr. with boiling ethylene glycol in which sodium had been dissolved caused general breakdown. Attempted reduction of the salt (XX) with sodium in liquid ammonia, both with and without ammonium chloride in the solvent, gave starting material as the only isolable solid. However, in agreement with van Tamelen *et al.*,[18] reduction of the *trans*-salt (XX) with sodium and ethanol gave a mixture yielding the base which had been prepared earlier from the salt (XX) by catalytic hydrogenation. This result supports our earlier assignment of the stereochemistry (VII) to this base since reduction with sodium and alcohol is known [19] to give the thermodynamically more stable product. The base (XXI) must be formed at most in small amount by the sodium–ethanol reduction as we were unable to isolate it from the reaction mixture as the picrate despite the ease of crystallisation and sparing solubility of this salt.

All the foregoing evidence and that given in Part III [20] interlocks, and the stereochemistry (XXII; R = Me) for emetine is established. The minor alkaloids of Ipecacuanha have been directly related [21,20] with emetine by chemical means so that the stereochemistries of cephaeline (XXII; R = H), *O*-methylpsychotrine (XXIII; R = Me),

[17] Bohlmann, *Angew. Chem.*, 1957, **69**, 641; *Chem. Ber.*, 1958, **91**, 2157; Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1956, **78**, 6417.
[18] van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1957, **79**, 4817; cf. van Tamelen and Hester, *ibid.*, 1959, **81**, 507.
[19] Barton and Robinson, *J.*, 1954, 3045 and refs. therein.
[20] Battersby, Binks, and Davison, *J.*, 1959, 2704.
[21] Reviewed by Janot, " The Alkaloids," ed. Manske and Holmes, Academic Press, Inc., New York, 1953, Vol. III, p. 363;

psychotrine (XXIII; R = H), and emetamine [22] (XXIII; R = Me with ring B aromatised) are now known.

It should be emphasised that the absolute configuration at position 10 of emetine (XXII; R = Me) is the same as that at the corresponding carbon atom in all those indole alkaloids which are thought to be biosynthesised from tryptophan and phenylalanine or their equivalents.[23,24] This carbon atom is marked * in corynantheine [15,24] (XXIV) and yohimbine [25] (XXV) which are given as examples. We have discussed elsewhere [1] the considerable biogenetic interest of this correlation between the Ipecacuanha and indole alkaloids.

After our publication of the preliminary account of most of the foregoing work,[26] van Tamelen, Aldrich, and Hester reported briefly [18] the synthesis of the *trans*-base (VII). By correlating it with an intermediate used in the Russian synthesis of emetine,[27] and by using the determination from this laboratory of the absolute configuration at position 1 of emetine [28] in conjunction with further optical studies, they also derived the stereochemistry (XXII) for emetine, in agreement with our work. The *trans*-arrangement at positions 10 and 11 of emetine was subsequently given further support by Brossi *et al.*[29] using a different approach, and recently [31] Ban and his co-workers have published results which are in agreement with ours concerning the relative and absolute stereochemistry at position 1'.

Experimental

For general directions see Part I.[2]

Clemmensen Reduction of Protoemetine (V).—An ethereal solution of protoemetine, freshly recovered from the perchlorate monohydrate (0·15 g.), was shaken with 6N-hydrochloric acid (15 ml.), and the acidic solution was heated with amalgamated granular zinc (1·1 g.) for 0·5 hr. on the water-bath, kept at room temperature for 24 hr., heated again on the water-bath for 24 hr., decanted from the excess of zinc, and evaporated to dryness. The residue was dissolved in water and made strongly alkaline with sodium hydroxide. Ether-extraction yielded a gum (0·1 g.) which was converted into the perchlorate in aqueous ethanol; a mixture of partly crystalline lumps and fine crystals was precipitated. The latter were separated by hand and after recrystallisation from water had m. p. 198—199°, unchanged in admixture with dihydroprotoemetine perchlorate [3] (as II; R = CH_2·OH); the two samples of perchlorate had identical infrared spectra (in Nujol).

Wolff–Kishner Reduction of Protoemetine (V).—Anhydrous protoemetine semicarbazone [3] (425 mg.) was added to a warm (60°) solution of potassium hydroxide (2·5 g.) and anhydrous hydrazine (5 ml.) in dry ethylene glycol (10 ml.). The mixture was protected against moisture and was heated at 155° for 5 hr. After the cooled solution had been diluted with water (50 ml.), it was extracted thrice with ether, each ether layer being washed twice with water. Evaporation of the dried ethereal solution left a gum (315 mg.) which, in aqueous ethanol, was converted into the perchlorate. *Deoxyprotoemetine* (VII) *perchlorate* separated as prisms (398 mg., 87%), m. p. 105—107° to a resin which flowed at 176—177°, unchanged by recrystallisation from aqueous ethanol (Found, in sample dried first at 78° and then to constant weight at 100°: C, 56·6; H, 7·7; N, 3·8. $C_{19}H_{30}O_6NCl$ requires C, 56·5; H, 7·5; N, 3·5%), $[\alpha]_D^{20}$ −41·0° (*c* 5·25 in aqueous ethanol made from 70 ml. of ethanol and 5 ml. of water).

[22] Battersby, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," The Chemical Society, London, 1955, p. 36 and refs. therein.
[23] Woodward, *Nature*, 1948, **162**, 155; Robinson, *ibid.*, 524; Saxton, *Quart. Reviews*, 1956, **10**, 108; Bose, *Chem. and Ind.*, 1958, 1690.
[24] Wenkert and Bringi, *J. Amer. Chem. Soc.*, 1958, **80**, 3484; 1959, **81**, 1474.
[25] Klyne, *Chem. and Ind.*, 1953, 1032.
[26] Battersby and Cox, *Chem. and Ind.*, 1957, 983.
[27] Evstigneeva, Livshits, Bainova, Zakharkin, and Preobrashenski, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 1467.
[28] Battersby, Binks, Davidson, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982.
[29] Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *ibid.*, 1958, 491; cf. Osbond, *ibid.*, 1959, 257.
[30] Carr and Pyman, *J.*, 1914, **105**, 1591.
[31] Ban, Terashima, and Yonemitsu, *Chem. and Ind.*, 1959, 568, 569.

Deoxyprotoemetine base was recovered into ether as usual and was distilled at 120° (bath)/0·05 mm. for determination of its infrared spectrum (in CS_2) which showed $\nu_{max.}$ 2745 cm.$^{-1}$, no OH or C=O bands. The distilled base subsequently crystallised and had m. p. 58—59°, but the amount available was insufficient to allow recrystallisation; it had $[\alpha]_D^{20}$ −75·3° (*c* 1·13 in ethanol).

Treatment of Emetine under Wolff–Kishner Conditions.—Emetine, freshly recovered from the pure hydrochloride, had $[\alpha]_D^{20}$ −49·2° ± 1° (*c* 3·56 in chloroform) (lit.,[30] −50°). This base (0·66 g.) was heated as was protoemetine above with potassium hydroxide (3·5 g.) and anhydrous hydrazine (3·5 ml.) in dry ethylene glycol (7 ml.). The non-phenolic bases (0·59 g.), recovered as above, were dissolved in a slight excess of hydrochloric acid, and the solution was diluted to 40 ml. After the addition of ammonium bromide (1 g.), emetine hydrobromide crystallised (0·799 g., containing 7·1% of water), m. p. 248—256° unchanged on admixture with authentic emetine hydrobromide of the same m. p. Part of the base recovered from the above hydrobromide had $[\alpha]_D^{18}$ −46·5° ± 1° (*c* 3·55 in chloroform) and its infrared spectrum (in $CHCl_3$) was superimposable on that of authentic emetine base; the remaining base was converted by Carr and Pyman's method [30] into *N*-benzoylemetine (62% yield), m. p. 181·5—182·5° unchanged on admixture with authentic *N*-benzoylemetine of the same m. p. The preparation of the latter was carried out on the same scale as the preceding benzoylation (60% yield). The two samples of *N*-benzoylemetine had identical infrared spectra (in Nujol).

Mercuric Acetate Oxidation of Deoxyprotoemetine (VII).—The base (VII), recovered from its perchlorate (181 mg.), was dissolved in warm 15% aqueous acetic acid (2 ml.) and added to a warm solution of mercuric acetate (0·41 g.) and potassium acetate (24 mg.) in 15% aqueous acetic acid (1 ml.). After this solution had been heated under reflux for 1·5 hr., it was cooled and filtered, and the pad was washed with water and ethanol. The filtrate was boiled and then allowed to cool during 20 min. under a pressure of hydrogen sulphide. 2N-Hydrochloric acid was added, the solution was boiled, and the treatment with hydrogen sulphide was repeated. The sulphides were filtered off (" Filtercel ") and washed with water and ethanol, and the filtrate was concentrated to 2 ml. Addition of 60% perchloric acid (5 drops) caused separation of *dehydrodeoxyprotoemetine perchlorate* (XX) which was recrystallised from aqueous ethanol and gave prisms (149 mg.), m. p. 165—166° (Found: C, 57·1; H, 7·4. $C_{19}H_{28}O_6NCl$ requires C, 56·8; H, 7·0%), $[\alpha]_D^{20}$ +79° (*c* 1·22 in aqueous ethanol made from 70 ml. ethanol and 5 ml. water), $\lambda_{max.}$ 250, 310, 355, $\lambda_{min.}$ 240, 275, 330 mμ (log ε 4·33, 3·97, 4·01, 4·28, 3·33, 3·77 respectively in EtOH), changed to $\lambda_{max.}$ 296, $\lambda_{min.}$ 280 mμ (log ε 3·81, 3·78 respectively) when the solution was made alkaline with sodium hydroxide; it had $\nu_{max.}$ 1647 cm.$^{-1}$ (C=N$^+$), no band in 2750 ± 10 cm.$^{-1}$ region (in $CHCl_3$).

Hydrogenation of Dehydrodeoxyprotoemetine Perchlorate (XX).—A solution of this salt (80 mg.) in 4 : 1 ethanol–water (12·5 ml.) was shaken with hydrogen and platinum at 18°/747 mm.; uptake (1·01 mol.) ceased after 17 min. The catalyst was filtered off and the solution concentrated to 2 ml. Deoxyprotoemetine perchlorate (VII) crystallised (67 mg.), having m. p. behaviour as recorded above, unchanged on admixture with authentic material. The infrared spectrum (in Nujol) and the *X*-ray powder photograph were identical with those of deoxyprotoemetine perchlorate (VII).

Lactone (XI) *of* erythro-β*γ-Diethyl-*δ*-hydroxyvaleric Acid.*—*cis*-3,4-Diethylcyclopentanone (2·78 g.) was added to a solution of perbenzoic acid (3·86 g.) in moist chloroform (75 ml.) and after 7 days at room temperature the solution was shown by titration of an aliquot part to contain 0·02 g. of perbenzoic acid. Ether (200 ml.) was then added and this solution was shaken with 5% sodium carbonate solution (3 × 20 ml.). Evaporation of the organic layer left an oil which in ethanol (100 ml.) was treated with N-sodium hydroxide (66 ml.) and water (100 ml.). This solution was extracted with ether (3 × 100 ml.), and the aqueous layer and washings were acidified to Congo Red with hydrochloric acid and re-extracted with ether (3 × 150 ml.). Evaporation of the dried ethereal solution and distillation of the residue gave the crude lactone (XI) (2·1 g.), b. p. 146—148°/20 mm. The ultraviolet spectrum of this product suggested strongly that it was contaminated with benzoic acid and for purification it was fractionated on a column of silica gel. Elution with benzene–chloroform (1 : 1) yielded the best sample of the *cis-lactone* (XI), though still not completely pure, which was redistilled for analysis (Found: C, 68·7; H, 9·6. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

Ethyl erythro-β*γ-Diethyl-*δ*-bromovalerate* (XII).—A solution of the foregoing crude lactone (4·66 g.) in absolute ethanol (20 ml.) was saturated at 0° with dry hydrogen bromide and then

kept at 5° for 19 hr. The mixture was poured on ice and water, and the products were extracted quickly into ether. After the ethereal solution had been washed with 15% potassium carbonate solution (20 ml.) and water, it was dried and evaporated. The residue yielded a fraction (5·5 g.), b. p. 133—134°/13 mm., containing the bromo-ester (XII) (Found: Br, 24·8%; corresponding to 82% of the bromo-ester).

cis-1-(3,4-*Dimethoxyphenethyl*)-4,5-*diethyl*-2-*oxopiperidine* (XIII).—The foregoing crude bromo-ester (3·52 g.), 3,4-dimethoxyphenethylamine (3·22 g.), potassium carbonate (1·63 g.), potassium iodide (1 crystal), and butan-1-ol (10 ml.) were heated together at 80° under nitrogen for 4 hr. and then under reflux for a further 42 hr. After addition of water to the cooled solution, it was extracted thrice with ethyl acetate, and the combined organic layers were washed with 0·5N-hydrochloric acid (2 × 20 ml.) and water. Evaporation of the dried ethyl acetate solution left the neutral products which were distilled at 5 × 10^{-5} mm. After a small fraction up to 130° (bath), the *oxopiperidine* (XIII) distilled at 140—190° (bath), mainly at 170°. This product is sufficiently pure for use in the next stage, but part was purified on a silica gel column, with chloroform–benzene (1 : 1) for elution. Redistillation of the eluate in a short-path still gave the pure oxopiperidine (XIII) (Found: C, 71·9; H, 9·3; N, 4·0. $C_{19}H_{29}O_3N$ requires C, 71·45; H, 9·15; N, 4·4%).

cis-5,11b-*Dehydro*-2,3-*diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide* (XIV; $X^- = I^-$) *and Perchlorate* (XIV; $X^- = ClO_4^-$).—Freshly distilled phosphoryl chloride (20 ml.) was heated under reflux for 1 hr. in anhydrous toluene (50 ml.) containing the foregoing oxopiperidine (2 g.). The cooled solution was poured on ice, and the separated toluene layer was extracted twice with dilute hydrochloric acid. The combined aqueous solution was extracted thrice with ether, made strongly alkaline with potassium hydroxide, and re-extracted with ether, each extract being washed with water. The combined ethereal solution was then extracted with 0·5N-hydrochloric acid (20 + 10 ml.), and concentrated potassium iodide solution was added to the combined acidic extracts. Recrystallisation of the precipitate from acetone–ether gave the *quinolizinium iodide* (XIV; $X^- = I^-$) (1·27 g.), m. p. 159—160° (Found: C, 52·8; H, 6·5; N, 3·4. $C_{19}H_{28}O_2NI$ requires C, 53·2; H, 6·6; N, 3·3%).

The iodide (0·1 g.) was treated with potassium hydroxide solution, and the iso-base (XV) was extracted into ether and recovered from it as a gum by evaporation at *ca.* 20°. A solution of this gum in ethanol was treated with 60% perchloric acid (5 drops) to yield the *quinolizinium perchlorate* (XIV; $X^- = ClO_4^-$) (88 mg.) which, recrystallised from aqueous ethanol, had m. p. 171—172° (Found: C, 56·9; H, 7·1. $C_{19}H_{28}O_6NCl$ requires C, 56·8; H, 7·0%), $\nu_{max.}$ (in $CHCl_3$) 1647 $cm.^{-1}$ ($C{=}N^+$).

cis-2,3-*Diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizine* (VI).—(a) *Catalytic reduction.* The foregoing perchlorate (338 mg.) was hydrogenated (uptake 1·02 mol.) and worked up as described for the reduction of dehydrodeoxyprotoemetine perchlorate above, to give a crystalline perchlorate (294 mg.). This was recrystallised from aqueous ethanol to yield the *quinolizine perchlorate* (as VI) as needles (250 mg., 74%), m. p. 198—199° (Found: C, 56·8; H, 7·5; N, 3·9. $C_{19}H_{30}O_6NCl$ requires C, 56·5; H, 7·5; N, 3·5%), $\lambda_{max.}$ 232·5, 283·5, $\lambda_{min.}$ 219, 265 mμ (log ε 4·01, 3·54, 3·91, 3·17 respectively) in EtOH.

For infrared comparison with deoxyprotoemetine, the base was recovered from the pure perchlorate and distilled as described above for deoxyprotoemetine.

(b) *Reduction by sodium borohydride.* A solution of the salt (XIV; $X^- = ClO_4^-$) (31 mg.) in methanol (5 ml.) was treated with sodium borohydride (13 mg.), acidified, and made strongly alkaline with potassium hydroxide. The product was extracted into ether, recovered by evaporation, and converted into the perchlorate in ethanol. The crystals obtained (23 mg.) recrystallised from aqueous ethanol to give the salt (17 mg.) obtained by method (*a*) above, m. p. and mixed m. p. 198—199°.

trans-3,4-*Diethylcyclopentanone* (XVI).—The crude ketone obtained by Koelsch and Stratton's simplified procedure [11] was redistilled and part (20 g.) was converted into the semicarbazone as usual. Recrystallisation from ethanol gave the pure semicarbazone (24·5 g.), m. p. 205—207° (decomp.) [lit.,[11] 202·5—206° (decomp.); lit.,[15] 208·5—209·5° (corr.)]. This was heated on the steam-bath for 1·5 hr. with concentrated hydrochloric acid (242 ml.) and water (215 ml.), cooled, and extracted thrice with ether, each ether layer being washed once with 5% potassium carbonate solution and once with water. After the combined ethereal solution had been dried, it was evaporated and the residue distilled completely at 85—86°/13 mm., to give pure *trans*-3,4-diethylcyclopentanone (14·8 g.).

Lactone (XVII) *of* threo-βγ-*Diethyl*-δ-*hydroxyvaleric Acid.*—This was prepared from *trans*-diethylcyclopentanone (13·76 g.) as described above for the *erythro*-lactone (XI); the threo-*lactone* had b. p. 140°/20 mm. It was purified on a column of silica gel; after elution with benzene and benzene–chloroform (1 : 1), the lactone was obtained by elution with chloroform. Distillation in a short-path still at 170° (bath)/30 mm. gave the analytical sample (Found: C, 68·8; H, 10·6. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

trans-1-(3,4-*Dimethoxyphenethyl*)-3,4-*diethyl*-2-*oxopiperidine* (XIX).—Treatment of the above lactone (9·75 g.) as described for the *erythro*-isomer yielded ethyl *threo*-βγ-diethyl-δ-bromovalerate (XVIII), b. p. 135—137°/14 mm. (12·9 g.) (Found: Br, 30·5. Calc. for $C_{11}H_{21}O_2Br$: Br, 30·2%). Part of this (3·19 g.) was used for the reaction with 3,4-dimethoxyphenethylamine as described above for the *cis*-isomer (XIII). The distilled product (3·5 g.), b. p. 180° (bath)/1·5 × 10^{-4} mm., was further purified on a column of silica gel by elution with benzene, benzene–chloroform (1 : 1), and chloroform. The last solvent yielded the trans-*oxopiperidone* (XIX) which was redistilled for analysis (Found: C, 70·9; H, 9·1; N, 4·1. $C_{19}H_{29}O_3N$ requires C, 71·45; H, 9·15; N, 4·4%). This distillate crystallised from ether–light petroleum and had m. p. 57—58°. The crystal form was lost completely when the solid was dried in a vacuum-desiccator at room temperature; this suggests that solvent of crystallisation is essential.

trans-5,11b-*Dehydro*-2,3-*diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* (XX).—This preparation followed that of the *cis*-isomer (XIV). The *trans*-oxopiperidine (XIX) (1·04 g.) yielded the trans-*quinolizinium perchlorate* (XX) as prisms or metastable needles (1·12 g.) which after recrystallisation from aqueous ethanol (charcoal) had m. p. 165—166° after slight previous sintering (Found: C, 56·9; H, 7·2; N, 3·6. $C_{19}H_{28}O_6NCl$ requires C, 56·8; H, 7·0; N, 3·5%), $\nu_{max.}$ (in $CHCl_3$) 1647 cm.$^{-1}$ (C=N$^+$).

trans-2,3-*Diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizine* (VII).—(a) *Catalytic reduction.* The foregoing salt (202 mg.) was hydrogenated (uptake 1·01 mol.) as described for the *cis*-isomer (XIV; $X^- = ClO_4^-$), to give the trans-*quinolizine perchlorate* (as VII), m. p. 211—213° (from aqueous ethanol) (148 mg.) (Found: C, 56·8; H, 7·8; N, 3·8. $C_{19}H_{30}O_6NCl$ requires C, 56·6; H, 7·5; N, 3·5%), $\lambda_{max.}$ 233, 285, $\lambda_{min.}$ 220, 256 (log ε 3·8, 3·54; 3·76, 2·61 respectively) in EtOH.

For infrared comparison with deoxyprotoemetine, the base was recovered from the pure perchlorate and distilled as for the *cis*-isomer.

(b) *Reduction by sodium borohydride.* The *trans*-salt (XX) (31 mg.) was reduced as for the *cis*-isomer, to give a crystalline perchlorate (27 mg.), m. p. 207—208° raised to 210—212°, alone or on admixture with the product from (*a*) above, by one recrystallisation from aqueous ethanol.

Reduction of the trans-*Salt* (XX) *with Zinc and Acetic Acid.*—A solution of this salt (887 mg.) in 50% aqueous acetic acid (50 ml.) was stirred at 60° with zinc dust (4 g.) for 24 hr. More zinc (3 g.) and glacial acetic acid (10 ml.) were then added and the stirring was continued for a further 70 hr. The solution was separated by decantation and, after the unused zinc had been washed with aqueous ethanol, the combined solutions were evaporated to dryness. The residue was dissolved in an excess of dilute hydrochloric acid, and the solution was extracted with ether. The aqueous solution was made strongly alkaline with sodium hydroxide and extracted thrice with ether, and the combined ethereal solution was extracted with 0·4N-hydrochloric acid (2 × 20 ml.). Evaporation of these acidic extracts left a solid which was shown by ultraviolet absorption measurements to contain less than 25% of starting material. It was dissolved in methanol (20 ml.), sodium borohydride (0·2 g.) was added portionwise in 5 min., and the solution was warmed at 50° for 0·5 hr. Water (30 ml.) was then added, the methanol was removed under reduced pressure, and, after the addition of a large excess of sodium hydroxide, the mixture was extracted with ether. Evaporation of the ethereal solution left a gum (587 mg.) which was converted into its perchlorate in aqueous solution as usual. This partly crystalline salt recrystallised from ethanol, to give the *trans*-diethylquinolizidine (VII) perchlorate (288 mg.), m. p. 205—208°, raised to 208—211°, after previous sintering in each case, on admixture with the pure salt from the foregoing experiment, section (*a*).

The bases were recovered as usual from the above ethanolic mother-liquors and were treated in ethanol with picric acid (0·4 g.); crystals separated (216 mg.), having m. p. 197—199°. These were recrystallised from methanol to give the trans-2,3-*diethylquinolizidine* (XXI) *picrate* as rhombs, m. p. 199—200° (Found: C, 56·9; H, 5·9. $C_{25}H_{32}O_9N_4$ requires C, 56·4; H, 6·05%).

A solution of the picrate (176 mg.) in chloroform was passed over alumina, and the column was eluted with chloroform. Evaporation of the eluate left the free base (XXI) as a thin gum (98 mg.). Part was distilled at 120°/0·05 mm. for analysis (Found: OMe, 20·5. $C_{19}H_{29}O_2N$ requires 2OMe, 20·4%). A further portion (9·7 mg.) was heated on the steam-bath with acetic anhydride (1 ml.) for 1 hr., and the excess of anhydride was then evaporated. The residue was separated into a neutral (trace) and a basic fraction (8·2 mg.) by partition as usual between ether and acid.

Mercuric Acetate Oxidation of the Base (XXI).—A solution of the foregoing base (23 mg.) and mercuric acetate (70 mg.) in 15% aqueous acetic acid (2 ml.) was heated under reflux for 6 hr. The mixture was worked up as described above for deoxyprotoemetine, a crystalline perchlorate (24 mg.) being obtained. This recrystallised from aqueous ethanol (charcoal), to give the *trans*-salt (XX) (17 mg.), m. p. and mixed m. p. 165—167°. The infrared spectrum (in Nujol) of this product was identical with that of the authentic *trans*-salt (XX).

Reduction of the trans-*Salt* (XX) *with Sodium and Alcohol.*—A solution of the salt (0·2 g.) in hot ethanol (30 ml.) was added dropwise to anhydrous ethanol (25 ml.) in which sodium (2 g.) was dissolving. After 15 min., more sodium (1 g.) was added and the solution was heated under reflux while addition of the solution containing the salt (XX) was continuing; the addition was carried out in 45 min. and all the sodium had dissolved after 1·5 hr. Water was added to the cooled solution, which was freed from ethanol by evaporation and then extracted with ether. Evaporation of the extracts left a gum (135 mg.). This was converted into the perchlorate in ethanol, and the crystals were collected (95 mg.), m. p. 170—182°; by five recrystallisations from ethanol, these yielded the *trans*-quinolizidine (VII) perchlorate (18 mg.), m. p. 203—205° raised to 207—210° in admixture with the sample of this salt prepared under (*a*) above. The two samples had identical infrared spectra (in Nujol).

Attempts were made to isolate the picrate of the base (XXI) from the various mother-liquors obtained in the above fractional crystallisation. Only a solid (47 mg.), m. p. 167—173° (decomp.), was obtained; the m. p. was raised to 172—176° by recrystallisation from ethanol. Recovery of the base from part of this picrate by passing a solution of it in chloroform over alumina gave a clear gum. This gave an infrared spectrum which was different from that given by the base (XXI).

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