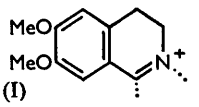
347. *Ipecacuanha Alkaloids. Part II.* The Structure of Protoemetine and a Partial Synthesis of (−)-Emetine.*

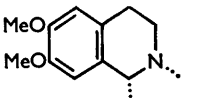
By A. R. Battersby and B. J. T. Harper.

Protoemetine, a new alkaloid from ipecacuanha root, is shown to have the structure (V; R = CHO) and its properties are described. A partial synthesis of (−)-emetine from protoemetine has been achieved, thus showing that the two alkaloids have the same stereochemistry. The biogenetic significance of protoemetine is discussed.

It was shown in the preceding paper that ipecacuanha root contains a new, optically active alkaloid which, because of its conversion into emetine (below) and for the biogenetic reasons discussed below, was named protoemetine. The instability of the new base prevented molecular-weight studies; as a result, the following discussion of its chemistry starts with the assumption that its empirical formula, $C_{19}H_{27}O_3N$, is also the molecular formula. This will be subsequently justified.



(I)



(II)

As reported briefly in part,[1] protoemetine contains two methoxyl groups and the Kuhn–Roth oxidation yielded 53% of the theoretical amount of acetic acid from one *C*-methyl group; there is no *N*-methyl group. A negative Labat test showed the absence of methylenedioxy-groups. The ultraviolet absorption is characteristic of a veratrole nucleus and indicates that only one such residue is present in the molecule. Moreover, the alkaloid was readily dehydrogenated by mercuric acetate, which is known to convert many cyclic amines into the corresponding imines [2] and in particular to dehydrogenate tetrahydro*iso*quinolines to the corresponding 3 : 4-dihydro*iso*quinolines.[3] The ultraviolet absorption of

* Part I, preceding paper.

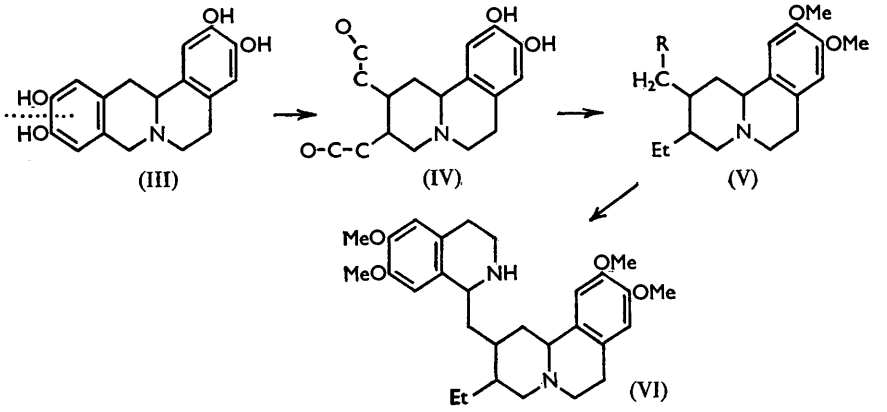
[1] Battersby, Davidson, and Harper, *Chem. and Ind.*, 1957, 983.
[2] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279, with earlier papers and refs. cited therein.
[3] Battersby and Binks, *J.*, 1958, 4333.

the amorphous product showed the typical pattern given by 3 : 4-dihydro-6 : 7-dimethoxy-*iso*quinoline salts (I). It is therefore very probable that the residue (II) is present in protoemetine.

The infrared spectrum of protoemetine perchlorate showed the absence of ester and alkene groups; however, the spectrum strongly indicated the presence of an aldehyde group. This was readily confirmed when the alkaloid gave a positive Tollens reaction and a crystalline semicarbazone. The presence of an aldehyde function explains the marked instability of protoemetine base which was noted in the preceding paper, and why the decomposition is accelerated by alkali.

Acetylation of protoemetine yielded an amorphous basic product, thus showing that the nitrogen atom is tertiary. Also, the basic strength of the alkaloid, as shown by a thermodynamic pK_a in water at 25° of 8·11 ± 0·01, is consistent with structures in which the nitrogen atom is common to two saturated rings. The above pK_a value can be compared with the apparent pK_a values for yohimbine and yohimbane (7·13 and 7·45 respectively), which were determined in 80% Methylcellosolve–water (the thermodynamic pK_a for strychnine [5] in water at 25° is 0·9 unit higher than the apparent pK_a for this alkaloid [6] determined in 80% Methylcellosolve–water). There was no reduction when the alkaloid-free base was shaken with hydrogen and platinum in ethanol, in keeping with the infrared studies above. However, the base perchlorate in the presence of sodium acetate absorbed one mol. of hydrogen with attack at the aldehyde group. No doubt the positive result obtained in the second experiment is due to the effect of acetic acid which is well known to assist hydrogenations.

There are many possible structures for protoemetine which will accommodate the evidence summarised above and the selection of the most probable one rests upon biogenetic considerations. Robinson [7] suggested that emetine (VI) arises by Woodward fission of one catechol residue in the norprotoberberine (III); in the scheme used here, the nature of the product (IV) is left purposely vague. Suitable reduction and *O*-methylation of this intermediate lead to the aldehyde (V; R = CHO) which by condensation with dihydroxy-

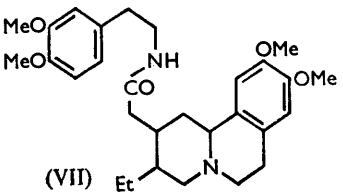


phenylalanine, decarboxylation, and *O*-methylation could reasonably give rise to emetine (VI). This scheme differs from the original one [7] in the order of the necessary reduction, methylation, and condensation steps, but, in effect, it was included in Robinson's proposals since they were not claimed to have sequential significance.

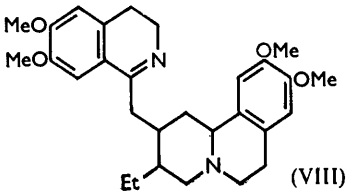
It is obvious that structure (V; R = CHO), $C_{19}H_{27}O_3N$, can explain all the properties

[4] Janot, Goutarel, Le Hir, Amin, and Prelog, *Bull. Soc. chim. France*, 1952, **19**, 1085.
[5] Everett, Openshaw, and Smith, *J.*, 1957, 1120.
[6] Prelog and Häfliger, *Helv. Chim. Acta*, 1949, **32**, 1851.
[7] Robinson, *Nature*, 1948, **162**, 524.

of protoemetine and attempts were made to confirm this structure by condensing protoemetine with 3 : 4-dimethoxyphenethylamine under the conditions of a Pictet–Spengler reaction. No emetine, *iso*emetine, or their derivatives could be isolated from the product.



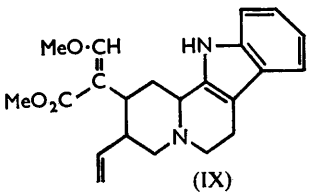
(VII)



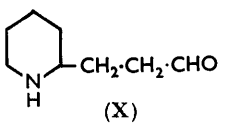
(VIII)

Protoemetine was, however, proved to have the structure (V; R = CHO) in the following way. An amorphous oxime (V; R = CH:N·OH) was readily prepared from the alkaloid and this was dehydrated with hot acetic anhydride to the crystalline nitrile (V; R = CN). Alkaline hydrolysis then converted the nitrile into the corresponding amino-acid (V; R = CO_2H); the same acid was obtained directly, though invariably in much lower yield, by the action of moist silver oxide on protoemetine under a variety of conditions. The acidic products from both routes were purified as the methyl ester (V; R = CO_2Me). When this ester was heated in a sealed tube with 3 : 4-dimethoxyphenethylamine, the crystalline amide (VII) was formed. A preferred route to this amide involved treatment of a suspension of the sodium salt of the amino-acid (V; R = CO_2H) in benzene with oxalyl chloride; [8] the acid chloride (V; R = COCl) so formed then reacted smoothly with 3 : 4-dimethoxyphenethylamine.

The amide (VII) was cyclised in high yield by the use of phosphoryl chloride in boiling toluene, and the crystalline product (VIII) was shown to be identical with natural *O*-methylpsychotrine by comparison of m. p., mixed m. p., and infrared absorption. Also, the crystalline hydrogen oxalates of the natural and the partially synthetic alkaloid had identical m. p., mixed m. p., infrared absorptions, optical rotations, and *X*-ray powder photographs. Since *O*-methylpsychotrine is known with certainty to have the structure (VIII), it follows from the foregoing transformations that protoemetine has the structure (V; R = CHO). *O*-Methylpsychotrine has previously been reduced [9] to (—)-emetine (VI), which is the naturally occurring form. Thus the partial synthesis of *O*-methylpsychotrine represents a partial synthesis of (—)-emetine; it also demonstrates conclusively that the



(IX)



(X)

stereochemistry at the three asymmetric centres of protoemetine is the same as that at the corresponding positions in emetine (VI). The importance of this correlation will be brought out in a forthcoming paper [10] on the stereochemistry of emetine.

The product from hydrogenation of protoemetine must now be assigned the structure (V; R = CH_2·OH) and is named dihydroprotoemetine; it was more readily obtained by reducing protoemetine with sodium borohydride in methanol.

The isolation of protoemetine gives strong support to the proposed mode of biogenesis of emetine [7] since it provides the link between the benzyl*iso*quinolines and the protoberberines on the one hand, and the more complex ipecacuanha alkaloids on the other. In

[8] Adams and Ulich, *J. Amer. Chem. Soc.*, 1920, **42**, 599.
[9] Pyman, *J.*, 1917, **111**, 419; Karrer, Eugster, and Rüttner, *Helv. Chim. Acta*, 1948, **31**, 1219; Battersby and Davidson, unpublished work.
[10] Battersby and Garratt, unpublished work.

this it is a close analogue of corynantheine (IX) in the indole series; this base, however, is the enol ether of an aldehyde. As there is now very strong evidence [11] that " pelletierine " does not have the structure (X) which was originally assigned to it, protoemetine remains as the only known aldehydic alkaloid.

Experimental

General directions are given in the preceding paper. Infrared spectra were determined as Nujol mulls unless otherwise stated.

Spectra.—The infrared spectrum of protoemetine perchlorate monohydrate showed peaks at 2810 cm.$^{-1}$ (aldehyde C–H), 1728 (aldehyde C:O) and 1622 cm.$^{-1}$ (aromatic ring). The ultraviolet absorption of the anhydrous salt in ethanol had $\lambda_{min.}$ 220 and 254, $\lambda_{max.}$ 232 and 283 mμ (log ε 3·85, 2·68, 3·92, 3·61 respectively).

Mercuric Acetate Dehydrogenation of Protoemetine (with G. C. Davidson).—A solution of freshly recovered protoemetine base (25 mg.) in 15% aqueous acetic acid (4 ml.) was boiled under reflux for 5½ hr. with hydrated sodium acetate (10 mg.) and mercuric acetate (0·2 g.). Hydrogen sulphide was then passed through the warm solution until the precipitation of the sulphides was complete. These solids were filtered off and the clear filtrate was evaporated to dryness. Part of the residue (1·2 mg.) was dissolved in water (100 ml.) for determination of the ultraviolet absorption, $\lambda_{min.}$ 229, 276, 326, $\lambda_{max.}$ 247, 303, 352 mμ [cf. the absorption of 3-(3 : 4-dimethoxyphenyl)-3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline hydrogen oxalate [3]].

Protoemetine Semicarbazone.—A mixture of protoemetine perchlorate monohydrate (0·6 g.) and semicarbazide hydrochloride (0·42 g.) was dissolved in water (6 ml.) and ethanol (1 ml.) at 40°. Hydrated sodium acetate (0·6 g.) was then added portionwise with swirling during 5 min. and the resultant solution was warmed on the water-bath for 15 min. The cooled solution was treated with ether (2 ml.) and made alkaline with ammonia; a gum was precipitated which crystallised (0·48 g.; m. p. 161—166°). Recrystallisation thrice from ethyl acetate gave *protoemetine semicarbazone*, m. p. 168—169° (Found: C, 64·2; H, 8·4; N, 15·2. $C_{20}H_{30}O_3N_4$ requires C, 64·1; H, 8·1; N, 14·95%).

Attempted Acetylation of Protoemetine.—Freshly recovered protoemetine (226 mg.) was heated with acetic anhydride (3 ml.) for 3 hr. at 90°. After distillation of the anhydride, the residue was separated as usual into a neutral (8 mg.) and a basic fraction (94 mg.). Much ether-insoluble polymer was formed.

Dihydroprotoemetine (V; R = CH_2·OH).—(a) *Use of borohydride.* A solution of protoemetine perchlorate (85 mg.) in methanol (5 ml.) was treated portionwise during 1 hr. with sodium borohydride (0·2 g.), then warmed at 60° for 5 min., diluted with water (30 ml.), and extracted thrice with ether, each organic layer being washed with water. Evaporation of the dried ethereal solutions yielded a gum (56 mg.) which afforded the *perchlorate of dihydroprotoemetine* from aqueous ethanol as prisms. After recrystallisation from water, these had m. p. 199—200° (Found: C, 54·2; H, 7·2. $C_{19}H_{30}O_7NCl$ requires C, 54·35; H, 7·2%), $\nu_{max.}$ (broad) 3550 cm.$^{-1}$ (OH) (no carbonyl band).

(b) *Catalytic preparation.* When anhydrous protoemetine perchlorate (13·48 mg.) and sodium acetate (11 mg.) were shaken in ethanol (10 ml.) with Adams platinum and hydrogen at 20·5°/743 mm., there was a steady uptake of hydrogen for the first 7 hr. This was followed by a very slow uptake (linear with time) for the next 23 hr. By extrapolating the slow linear uptake to zero time, the uptake in the more rapid phase was found to be 0·81 ml. (1·01 mol.). When the filtered solution was concentrated, dihydroprotoemetine perchlorate crystallised (7 mg.); after recrystallisation from water, this had m. p. 196—198°. Its infrared spectrum was identical with that of the foregoing product.

*2-Cyanomethyl-3-ethyl-*1 : 2 : 3 : 4 : 5 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizine* (V; R = CN).—A solution of protoemetine perchlorate monohydrate (754 mg.), hydrated sodium acetate (682 mg.), and hydroxylamine hydrochloride (414 mg.) in ethanol (28 ml.) and water (9 ml.) was heated under reflux for 1 hr. Hydroxylamine hydrochloride (0·3 g.) and hydrated sodium acetate (0·7 g.) were then added, followed by the same amounts again of these two reagents after a further 1 hour's heating; the reactants were then heated for 15 hr. After addition of water (27 ml.) to the mixture, the ethanol was evaporated and the aqueous solution

[11] Wibaut and Hirschel, *Rev. Trav. chim.*, 1956 **75**, 225; Bowman and Evans, *J.*, 1956, 2553.

was adjusted to pH 9 with aqueous potassium carbonate. The precipitated oil was extracted into ether, and the solution washed with water, dried, and evaporated to yield protoemetine oxime as a gum (586 mg.). This was heated under reflux with acetic anhydride (5 ml.) for 1 hr. and the anhydride was evaporated. The residue was partitioned between ether and dilute hydrochloric acid, and the aqueous layer, after basification with sodium hydroxide, was extracted thrice with ether. Evaporation of the dried ethereal solution left a gum (514 mg.) of which part (0·15 g.) was distilled at 160° (bath)/0·02 mm. The distillate crystallised from aqueous ethanol to give the *cyanomethyl derivative* (V; R = CN) as needles (135 mg.), m. p. 153·5—154° (Found: C, 72·7; H, 8·3. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·3%).

Methyl 3-*Ethyl*-1 : 2 : 3 : 4 : 5 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizin*-2-*ylacetate* (V; R = CO_2Me) *and the Corresponding Ethyl Ester* (V; R = CO_2Et).—(a) *From the corresponding nitrile.* The foregoing crude nitrile (364 mg.) was heated under reflux for 72 hr. with a solution (5 ml.) of potassium hydroxide (2·8 g.) in water (2 ml.) and ethanol (9 ml.). After addition of water (20 ml.) to the mixture, it was extracted thrice with ethyl acetate, some inorganic matter separating. This was filtered off, and the filtrate was acidified with hydrochloric acid and evaporated to dryness. The residue was dried overnight at room temperature over phosphoric oxide, and the amino-acid hydrochloride was extracted from the inorganic salts with anhydrous ethanol. Evaporation of the ethanol left a gum which was treated in anhydrous methanol (10 ml.) with concentrated sulphuric acid (0·4 ml.), heated under reflux for 4 hr., cooled, and poured on a mixture of ice and sodium carbonate. The precipitated base was extracted into ether, and the dried ethereal solution was evaporated to a gum (285 mg.). This crystallised from light petroleum (b. p. 40—60°) to give the *methyl ester* (V; R = CO_2Me) as needles (236 mg.), m. p. 96—98°. Distillation of this ester at 150° (bath)/0·01 mm., followed by three recrystallisations from light petroleum, gave the analytical sample, m. p. 98—99° (Found, in material dried at 56°: C, 69·6; H, 8·5. $C_{20}H_{29}O_4N$ requires C, 69·2; H, 8·4%), $[\alpha]_D^{20}$ −35·4° (*c* 2·82 in methanol), $\nu_{max.}$ (in CCl_4) 1740 (s) $cm.^{-1}$ (CO_2Me).

By substituting ethanol for methanol in the above esterification step, the corresponding *ethyl ester* was prepared. Distillation of the crude ester at 140° (bath)/5 × 10^{-4} mm. followed by three recrystallisations of the distillate from light petroleum (b. p. 40—60°) gave needles, m. p. 88—90° (Found, in material dried at 78°: C, 69·6; H, 8·6. $C_{21}H_{31}O_4N$ requires C, 69·75; H, 8·65%), $\nu_{max.}$ (in CCl_4) 1726 (s) $cm.^{-1}$ (CO_2Et).

(b) *Oxidation of protoemetine.* Protoemetine, freshly recovered from its perchlorate (80·8 mg.), was dissolved in 50% aqueous ethanol (12 ml.) and shaken in all for 2 hr. with silver oxide (from 0·4 g. of silver nitrate). Initially the reaction mixture was raised to 50° and shaking was continued without further heating for 1 hr. This process was repeated once. The suspension was then filtered, the solids were washed with warm water, and the filtrate was extracted thrice with ether. Evaporation of the aqueous layer left a gum which was dissolved in methanol (25 ml.); concentrated sulphuric acid (0·5 ml.) was added and the solution was heated under reflux for 2 hr., after which the amino-ester (9 mg.) was isolated and crystallised as above; it had m. p. and mixed m. p. 96—97°.

2-[(N-3 : 4-*Dimethoxyphenethylcarbamoyl*)*methyl*]-3-*ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizine* (VII).—(a) *From the ester* (V; R = CO_2Me). 3 : 4-Dimethoxyphenethylamine (0·2 g.) and the ester (V; R = CO_2Me) (50 mg.) were heated together in an evacuated sealed tube at 180° for 8 hr.; the mixture was then dissolved in ethyl acetate (20 ml.) and shaken with two portions (20 ml.; 10 ml.) of aqueous buffer made from 0·5M-KH_2PO_4 (11 vol.) and 0·5M-K_2HPO_4 (2 vol.), and the combined aqueous extracts were shaken with ethyl acetate (30 ml.). Evaporation of the combined organic solution left a crystalline residue (58 mg.) which was recrystallised from ethyl acetate, to give the amide (VII) as needles, m. p. 168—170°, raised to 169—170° on admixture with the sample below.

(b) *From the acid chloride* (V; R = COCl). A solution of the ester (V; R = CO_2Me) (117 mg.) in 2N-hydrochloric acid (5 ml.) was heated under reflux for 15 hr., then evaporated to dryness to leave the crystalline amino-acid hydrochloride. This was dried over phosphoric oxide at 100°/0·01 mm. for 3 hr. Part of the hydrochloride (117 mg.) in water (2 ml.) was treated with 0·1N-sodium hydroxide (6·34 ml., 2 equiv.), the solution then evaporated to dryness, and the finely powdered sodium salt, together with sodium chloride, dried as above. A suspension of this mixture (121 mg.) in dry benzene (5 ml.) was stirred at 0° while freshly distilled oxalyl chloride (0·038 ml., 1·5 equiv.) in benzene (1 ml.) was added during 5 min. After 15 min., the ice-bath was removed and the temperature of the mixture was raised to 20° during 1¾ hr.

3 : 4-Dimethoxyphenethylamine (0·3 ml.) was then added with stirring, and the mixture kept overnight. Addition of water (5 ml.) together with an excess of dilute hydrochloric acid gave a solution from which the benzene was evaporated. Some insoluble solid was filtered off and the filtrate was made alkaline with potassium carbonate. The precipitated solid (70 mg.) was recrystallised from ethyl acetate and from 50% aqueous ethanol, to give the *amide* (VII), m. p. 171·5—172·5° (Found: C, 69·5; H, 8·3. $C_{29}H_{40}O_5N_2$ requires C, 70·1; H, 8·1%), $\nu_{max.}$ 3440 and 1652 cm.$^{-1}$ (CO·NH).

Partial Synthesis of (+)-O-*Methylpsychotrine* (VIII).—A solution of the foregoing amide (23 mg.) in anhydrous toluene (2 ml.) was heated under reflux for 1 hr. with freshly distilled phosphoryl chloride (0·15 ml.). Water (10 ml.) was added to the cooled mixture, and the toluene layer was separated and shaken with dilute hydrochloric acid (5 ml.). The combined aqueous solutions were basified with sodium hydroxide and extracted thrice with ether. Evaporation of the dried ethereal solution left a gum (21 mg.) which crystallised from dry ether, to give *O*-methylpsychotrine (17 mg.), m. p. and mixed m. p. with the natural alkaloid 121—122·5°. The infrared spectra of the natural and the partially synthetic alkaloids were identical.

The partially synthetic base was converted into its hydrogen oxalate in the usual way to give the characteristic sheaves of needles, m. p. 151—155° (decomp.) unchanged on admixture with an authentic sample of *O*-methylpsychotrine hydrogen oxalate of the same m. p. (Found, in material dried at 110°: C, 56·6; H, 6·4. Calc. for $C_{33}H_{46}O_{12}N_2,2H_2O$: C, 57·0; H, 6·7%. Found, in authentic *O*-methylpsychotrine hydrogen oxalate dried under the same conditions: C, 56·4; H, 6·6%). $[\alpha]_D$ of the " synthetic " salt was +43·8° (*c* 2·10 in water); $[\alpha]_D$ of authentic *O*-methylpsychotrine hydrogen oxalate determined under the same conditions was +43·2° (*c* 2·02 in water). The identity of the natural and the partially synthetic hydrogen oxalate was further established as described on p. 1750.

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