763. *Ipecacuanha Alkaloids. Part VII.* The Structure of Emetamine: Stereospecific Synthesis of (±)-Emetamine and Indole Analogues of the Ipecacuanha Alkaloids.*

By A. R. Battersby, G. C. Davidson, and J. C. Turner.

It is established that emetamine (I) contains a 1-substituted isoquinoline residue by degrading it to a 1-isoquinolone. Similar degradation of a 1-substituted 3,4-dihydroisoquinoline yields the corresponding 3,4-dihydro-1-isoquinolone.

The controlled synthesis of (±)-emetamine (I) is described.

Analogues of the Ipecacuanha alkaloids are prepared in which the isolated isoquinoline system is replaced by a β-carboline residue.

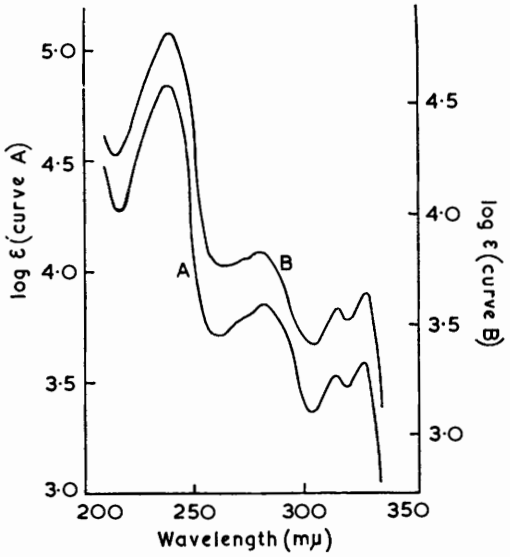
Emetamine, $C_{29}H_{36}N_2O_4$, is one of the minor alkaloids isolated [1] from Ipecacuanha which until recently [2] was not easy of access. For this reason its chemistry has not been fully examined and the available knowledge at the outset of the present work was as follows. Emetamine is a ditertiary base [3] which contains four hydrogen atoms fewer than emetine (II). It is reduced by sodium and ethanol to isoemetine which differs from emetine (II)

* Part VI, *J.*, 1960, 3474.

[1] Pyman, *J.*, 1917, **111**, 419.
[2] Battersby, Davidson, and Harper, *J.*, 1959, 1744.
[3] Brindley and Pyman, *J.*, 1927, 1067.

only in having the opposite configuration [4] at position 1'. On these grounds, Brindley and Pyman [3] proposed a structure for emetamine though they based it upon an incorrect structure for emetine. When their proposal is considered in relation to the correct emetine structure [5] (II), it leads to the structure (I) for emetamine.

Ahl and Reichstein [6] studied the dehydrogenation of emetine (II) over palladised charcoal at 190° which produced a complex mixture. A base was isolated from the products with properties in perfect agreement with those of emetamine, but no direct comparison could be made with the natural alkaloid. Accordingly, we repeated the dehydrogenation of emetine and isolated by countercurrent distribution a base having melting point, ultraviolet absorption, and partition ratio [7] agreeing closely with those of emetamine, but the optical rotation of the new base was opposite in sign to that of



Ultraviolet absorption spectra of (A) *emetamine* (I) *and* (B) *papaverine* (III), *in ethanol.*

emetamine (I). The nature of the new base has not been further examined since it was considered preferable to gain structural information from emetamine itself.

On the basis of structure (I), the ultraviolet absorption of emetamine should be the summation spectrum of a 1-alkyl-6,7-dimethoxyisoquinoline and a veratrole chromophore; in keeping with this, the spectrum of emetamine is very similar (see Figure) to that of papaverine (III). Degradative evidence was obtained by conversion of emetamine with hot benzyl chloride into its bisbenzylochloride (IV) which in alkaline solution gave the anhydro-base (V). This was readily oxidised by permanganate to afford the known [8] *N*-benzylisoquinolone (VI) which was identified by comparison with an authentic sample prepared [8] from papaverine (III). Oxidation of the anhydro-base (X) under identical conditions yielded *N*-benzylcorydaldine (XI); it is thereby proved that the 3,4-double bond in the isoquinolone (VI) from emetamine has not been introduced oxidatively. Thus the presence of a 1-substituted isoquinoline residue in emetamine is established and this result taken with the earlier work leaves no doubt about the structure (I) for this alkaloid.*

* The degradative work was outlined in a lecture " The Structure and Chemistry of Emetamine," A. R. Battersby, *Chem. Soc. Special Publ.* No. 3, " Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," London, 1955, p. 36.

[4] Pyman, *J.*, 1918, **113**, 222.

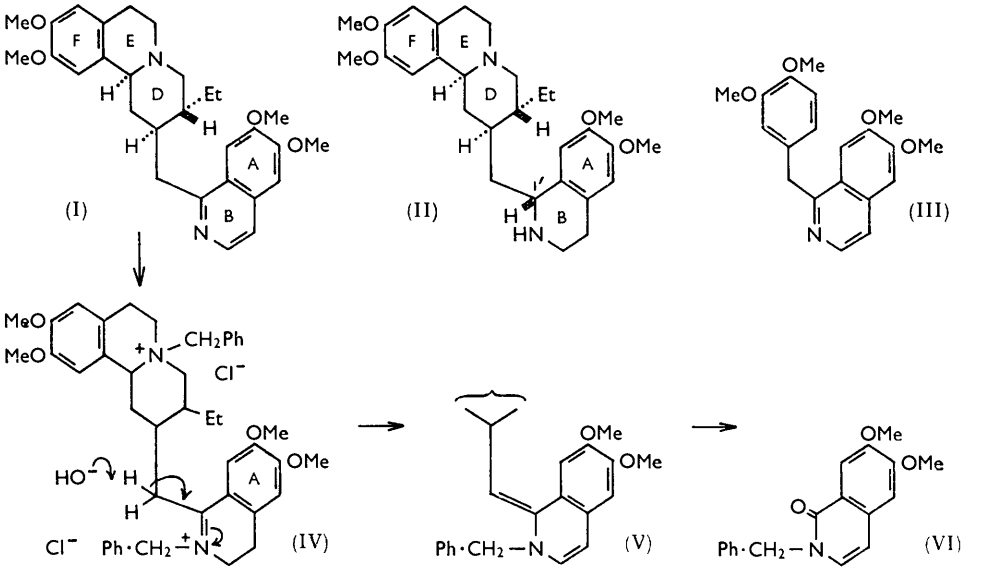
[5] Battersby and Openshaw, *J.*, 1949, 3207 and refs. therein; Pailer and Porschinski, *Monatsh.*, 1949, **80**, 94 and refs. therein.

[6] Ahl and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 366.

[7] Craig and Craig, " Techniques of Organic Chemistry," Ed. Weissberger, Interscience, New York, 1950, p. 171.

[8] Decker and Klauser, *Ber.*, 1904, **37**, 520.

The anhydro-base (X), used as a control substance in the foregoing work, was prepared as shown in the annexed scheme. Dehydrogenation of the 3,4-dihydroisoquinoline (VIII) over palladised charcoal gave the aromatised base (XIII), whilst borohydride reduction of the base (VIII) yielded the tetrahydroisoquinoline (XII). The same product (XII) was obtained when the isoquinolinium chloride (IX; $X^- = Cl^-$) was shaken with hydrogen and palladium. The rapid rate at which two mol. of hydrogen were absorbed suggests

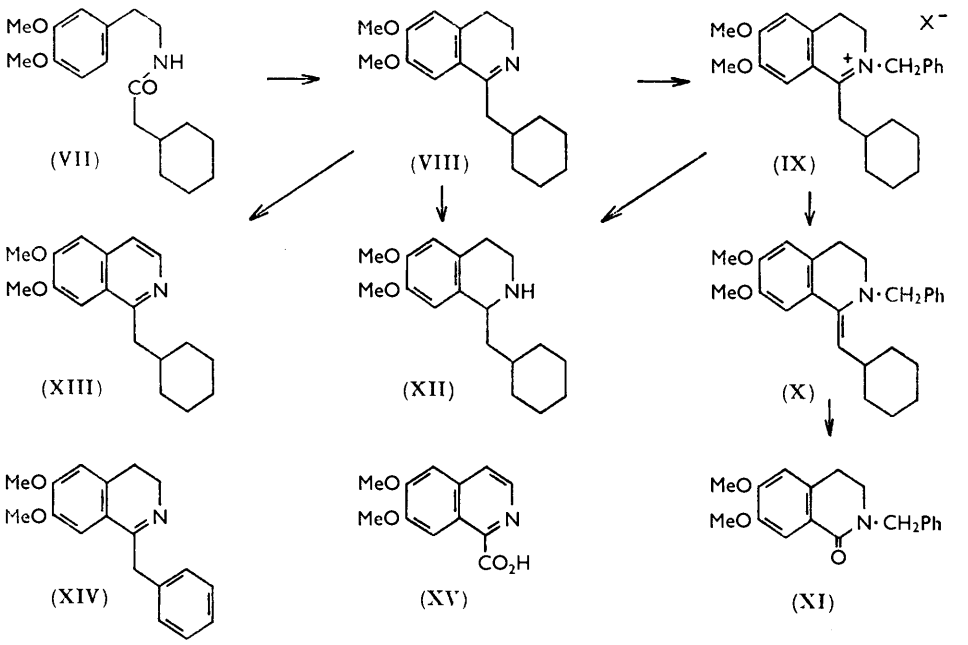


that debenzylation precedes saturation of the >C=N– system since hydrogenolysis of tertiary *N*-benzyl groups is normally slow under these conditions. Simple preparations of the compounds (XIV) and (XV) used in exploratory degradative work are described in the Experimental section; the amino-acid [9] (XV) was derived from the readily available [10] 6,7-dimethoxy-1-methylisoquinoline by condensation with benzaldehyde followed by oxidation.

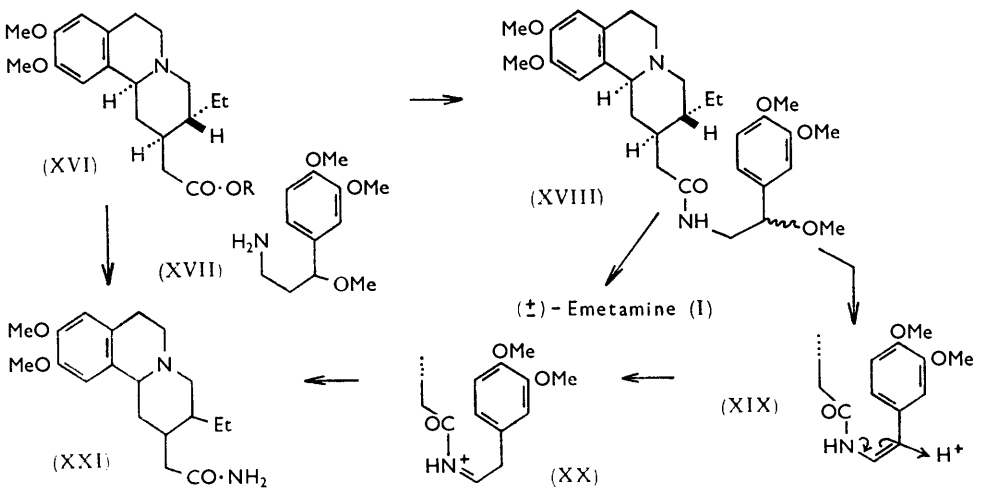
Battersby and Turner [11] described a stereospecific route to emetine (II) which as a result of previous conversions, also constituted a formal controlled synthesis of all the minor Ipecacuanha alkaloids with the exception of emetamine and protoemetine.[12] Because of the relationships discussed above, the stereochemistry about rings D and E of emetamine (I) is the same as obtains in isoemetine, which, for this part of the molecule, is the same as that established [13] for emetine (II). Thus the key intermediate (XVI; R = Et) prepared [11] for the synthesis of emetine is also the correct stereoisomer for the synthesis of emetamine. During our synthetic work, a brief account was given [14] of a Russian synthesis of (±)-emetamine in which the final steps are the same as ours. However, since that work, unlike ours, is not sterically controlled and since in addition the

[9] Carr and Pyman, *J.*, 1914, **105**, 1591.
[10] Späth and Polgar, *Monatsh.*, 1929, **51**, 190.
[11] Battersby and Turner, *J.*, 1960, 717; for other syntheses of emetine see: Evstigneeva and Preobrashenski, *Tetrahedron*, 1958, **4**, 223; Barash, Osbond, and Wickens, *J.*, 1959, 3530; Brossi, Baumann, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 1515; Grüssner, Jaeger, Hellerbach, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 2431; Burgstahler and Bithos, *J. Amer. Chem. Soc.*, 1960, **82**, 5466.
[12] Battersby and Harper, *J.*, 1959, 1748.
[13] Battersby, Binks, and Davidson, *J.*, 1959, 2704; Battersby and Garratt, *J.*, 1959, 3512; Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86; van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1959, **81**, 6214; Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *J.*, 1959, 3630; Ban, Terashima, and Yonemitsu, *Chem. and Ind.*, 1959, 568, 569.
[14] Evstigneeva, Breier, and Preobrashenski, *Doklady Akad. Nauk*, 1957, **117**, 227.

synthetic product was not compared with natural emetamine, we considered that our experiments should continue.



The ester (XVI; R = Et) was hydrolysed to the amino-acid (XVI; R = H) and as the mixed anhydride with ethyl hydrogen carbonate (*i.e.*, XVI; R = CO_2Et) was coupled with β,3,4-trimethoxyphenethylamine (XVII). A new asymmetric centre has been



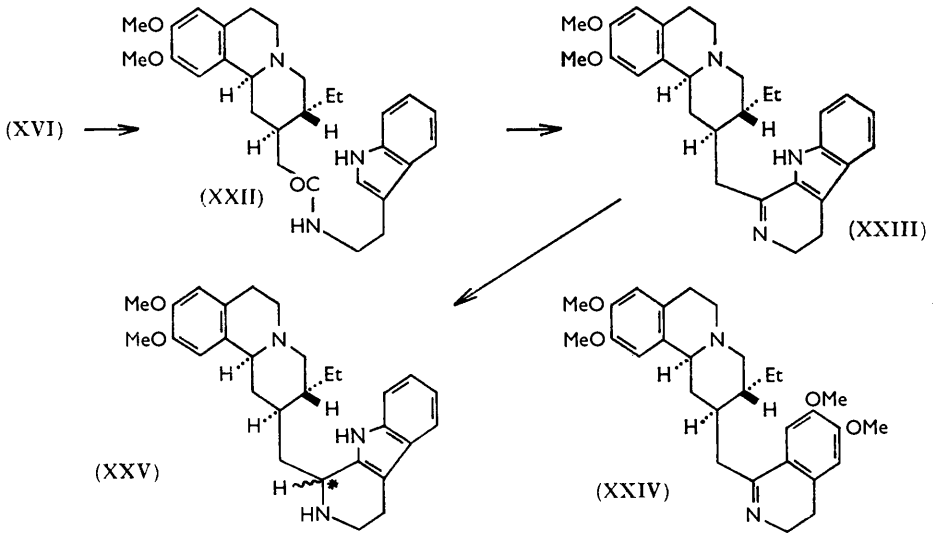
introduced in this step so that two diastereoisomers of the amide (XVIII) might be expected. One was isolated crystalline by chromatography and it is possible (see below) that the second is present in the amorphous products. The yield in the ring-closure of the crystalline amide (XVIII) was highly dependent on the conditions used but a study of the total reaction products from many reactions by ultraviolet analysis allowed a satisfactory procedure to be developed. Chromatography of the products then afforded (±)-emetamine

in 67% yield; the infrared spectrum of the synthetic base was identical with that of the natural alkaloid, as were the respective spectra of the hydrogen oxalate salts.

In experiments carried out before the best conditions for the cyclisation had been worked out, (±)-emetamine was accompanied by the amide (XXI). Its formation can be rationalised by considering acid-catalysed elimination of methanol from the methoxy-amide (XVIII). The product (XIX, without stereochemical implications for the double bond) could then accept a proton to yield the system (XX) which would be expected to be readily hydrolysed during the working-up of the reaction mixture with the formation of the amide (XXI). The structure of this by-product was confirmed by preparing it from the mixed anhydride (XVI; R = CO_2Et) by treatment with ammonia.

When the amorphous products from the preparation of the amide (XVIII) were cyclised with phosphoryl chloride a further small yield of (±)-emetamine (I) was obtained.

The synthetic work has been extended to the preparation of analogues of the Ipecacuanha alkaloids (*e.g.*, II) in which rings A and B are replaced by a β-carboline residue. From the known physiological effects of reduced benzoquinolizidine derivatives [15] and of



basic indole derivatives,[16] it seemed that materials such as the bases (XXV) and (XXIII) might be of pharmacological interest. The amino-acid (XVI; R = H) was condensed with tryptamine by the method used in the emetamine synthesis. Cyclisation of the resultant amide (XXII) with phosphoryl chloride gave the base (XXIII), which is the indole analogue of *O*-methylpsychotrine (XXIV). Catalytic hydrogenation of this product gave a mixture of bases, from which one isomer (XXV) was isolated as the crystalline hydrochloride. It is not known at present whether the configuration at the asterisk corresponds to that of the emetine (II) or the isoemetine series.

Experimental

For general directions, see Part I of this series.[2]

Dehydrogenation of Emetine [6] (II).—Emetine (3·4 g.) was heated with 20% palladised charcoal [17] (0·4 g.) at 180—190° (bath) in a stream of carbon dioxide; hydrogen (1·7 mol.) was evolved in 30 min. The cooled mixture was dissolved in ethanol, the solution was filtered and

[15] Brossi, Lindlar, Walter, and Schnider, *Helv. Chim. Acta*, 1958, **41**, 119.

[16] See, *inter al.*, Sexton, "Chemical Constitution and Biological Activity," Spon, London, 1949; Woodson, Youngken, Schlittler, and Schneider, "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology," Little, Brown and Co., Boston, U.S.A., 1957.

[17] Linstead and Thomas, *J.*, 1940, 1130.

the filtrate was evaporated. Distillation of the residue at 0·01 mm. gave one fraction distilling up to 165° (bath) and a second distilling at 165—225°. The latter (1·63 g.) was fractionated by countercurrent distribution in the system used [2] to isolate emetamine from Ipecacuanha. Recovery of the base from the " emetamine " fraction as before [2] gave a gum which was treated in ethanol (20 ml.) with hydrated oxalic acid (0·8 g.). Crystals separated (0·62 g.), m. p. 155—157° (decomp.), $[\alpha]_D^{19}$ +10·6° (*c* 4·0 in H_2O). The base was recovered from the hydrogen oxalate for a second distribution between ethyl acetate and 0·5M-phosphate buffer (pH 5·3). After 36 transfers, the contents of tubes 10—25 were worked up for base as usual [2] and the resultant gum (0·35 g.) crystallised from ethyl acetate to give a crystalline base, m. p. 142—143°. Part of this base (30 mg.) in ethanol (1 ml.) was treated with hydrated oxalic acid (18 mg.), giving the crystalline *hydrogen oxalate* which, recrystallised from ethanol, had m. p. 165—166° (decomp.), $[\alpha]_D^{18}$ +10·3° (*c* 17·1 in H_2O) (Found: C, 57·7, 57·4; H, 6·0, 6·4; N, 3·5. $C_{29}H_{36}N_2O_4,2C_2H_2O_4,2H_2O$ requires C, 57·2; H, 6·4; N, 4·05%). In parallel countercurrent distributions on natural emetamine and on the above base in the same solvent system under identical conditions, the two had the same partition ratio.

Emetamine base [1] has m. p. 155—156° (corr.); emetamine hydrogen oxalate [1] has m. p. 165—171° (corr.), $[\alpha]_D$ −6·0° (*c* 3·92 in H_2O).

Preparation and Oxidation of Emetamine Bisbenzylochloride (IV).—A solution of emetamine [2] (86 mg.) in freshly distilled benzyl chloride (2 ml.) was heated at 100° for 4 hr. and then evaporated to dryness. Trituration of the residue with ether (2 × 15 ml.) initiated crystallisation and the bisbenzylochloride (121 mg.) was collected and washed with ether. The solid was suspended in water (4 ml.) and was treated at 0° with 2N-sodium hydroxide (0·15 ml.) and rigorously purified dioxan (16 ml.) to afford a clear solution. This was vigorously stirred at 0° while a solution of potassium permanganate (56 mg.) in water (5 ml.) was added dropwise during 30 min. After the manganese dioxide had been coagulated by heat, it was filtered off and washed with water and hot acetone. Evaporation of the organic solvents from the filtrate gave an aqueous suspension of crystals which were collected (26 mg.; m. p. 159—161°). Sublimation at 150°(bath)/0·1 mm. gave the *N*-benzylisoquinolone (VI), m. p. and mixed m. p. with an authentic sample prepared [8] from papaverine 160—161·5°; the authentic sample had m. p. 162—163° in same bath. The ultraviolet spectra of the two samples (VI) were identical: $\lambda_{max.}$ 249, 282, 294, 312, 322, 336 mμ (log ε 4·67, 3·89, 3·95, 3·59, 3·65, 3·53 respectively) in EtOH.

N-(3,4-*Dimethoxyphenethyl*)-α-*cyclohexylacetamide* (VII).—Cyclohexylacetic acid [18] (5 g.) was warmed on the steam bath for 1 hr. with thionyl chloride (15 ml.), the excess of thionyl chloride was evaporated, and the residue, in anhydrous ether (25 ml.), was added dropwise to a stirred solution of 3,4-dimethoxyphenethylamine (12·8 g.) in ether (100 ml.). Water (100 ml.) and ethyl acetate (300 ml.) were then added and after equilibration and separation the ethyl acetate solution was shaken with an excess of 2N-hydrochloric acid and finally with water. Evaporation of the dried organic solution and crystallisation of the residue from toluene, gave the *amide* (VII) as plates (7 g.), m. p. 108—109° (Found, in material dried at 78°: C, 71·1; H, 8·1; N, 4·9. $C_{18}H_{27}NO_3$ requires C, 70·8; H, 8·9; N, 4·6%).

1-*Cyclohexylmethyl*-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (VIII).—A solution of the foregoing amide (4·87 g.) in dry toluene (15 ml.) was heated under reflux for 1 hr. with phosphoryl chloride (6·5 ml.), cooled, and treated with ice-water (30 ml.). The separated toluene layer was extracted with 2N-hydrochloric acid (3 × 30 ml.), and the combined aqueous solutions were basified with aqueous sodium hydroxide and extracted with ether (3 × 100 ml.). Evaporation of the dried extracts gave the dihydroisoquinoline (VIII) (4·7 g.). This was converted into the *perchlorate* by treatment with perchloric acid in ethanol; the crystalline precipitate, recrystallised from ethanol, had m. p. 153—155° (5·5 g.) (Found: C, 55·7; H, 6·9. $C_{18}H_{26}ClNO_6$ requires C, 56·0; H, 6·75%), $\lambda_{max.}$ 242, 301, 348, $\lambda_{min.}$ 223, 261, 319 mμ (log ε 4·30, 3·04, 4·03, 3·87, 2·88, 3·81 respectively) in H_2O.

The *base* was recovered from the perchlorate as usual and crystallised from ether as needles, m. p. 75—76°; these were sublimed at 130°(bath)/0·1 mm. for analysis (Found: C, 75·2; H, 8·6; N, 5·2. $C_{18}H_{25}NO_2$ requires C, 75·2; H, 8·8; N, 4·9%). The picrate was prepared in ethanol and had m. p. 204—205° (decomp.).

1-*Benzyl*-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (XIV).—This was prepared from 3,4-dimethoxyphenethylamine and phenylacetic acid as for the cyclohexyl analogue (VIII) above. The crude base (80% yield from the intermediate amide) was converted into the *hydrogen*

[18] Hope and Perkin, *J.*, 1909, **95**, 1360.

oxalate as above in ethanol and, recrystallised from ethanol, had m. p. 224—225° (decomp.) (Found: C, 64·5; H, 5·4; N, 3·6. $C_{20}H_{21}NO_6$ requires C, 64·7; H, 5·7; N, 3·8%).

2-Benzyl-1-cyclohexylmethyl-3,4-dihydro-6,7-dimethoxyisoquinolinium Iodide (IX; $X^- = I^-$).—The base (VIII) (2·49 g.) was heated with benzyl chloride (10 ml.) at 100—120° (bath) for 6·5 hr., and the mixture was then cooled. The precipitated crystals were collected and washed with ether but, because of their hygroscopic nature, the *iodide* was prepared by dissolving a portion of the chloride in 1 : 1 aqueous acetone and adding an excess of potassium iodide. Recrystallised from ethanol, the iodide (IX; $X^- = I^-$) had m. p. 208—209° (Found: C, 59·9; H, 6·3; N, 2·8. $C_{25}H_{32}INO_2$ requires C, 59·4; H, 6·4; N, 2·8%).

Oxidation of the Anhydro-base derived from the Salt (IX; $X^- = Cl^-$).—Purified dioxan (30 ml.) and 2N-sodium hydroxide (1·5 ml.) were added to a solution of the foregoing chloride (IX; $X^- = Cl^-$) (1 g.) in water (8 ml.). The resultant solution was stirred and treated dropwise at 0° during 30 min. with a solution of potassium permanganate (0·55 g.) in water (30 ml.). After the manganese dioxide had been coagulated by heat, it was removed by filtration, the solution was freed from organic solvents by evaporation, and the resultant aqueous suspension was extracted with ethyl acetate (3 × 50 ml.). The extracts were washed with dilute acid and saturated aqueous sodium carbonate, and were dried and evaporated. Crystallisation of the residue from ether gave 2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxoisoquinoline (XI) as needles (349 mg.), m. p. 101—102° (lit.,[19] m. p. 84°) * (Found, in material dried at 78°: C, 72·9; H, 6·7; N, 4·7. Calc. for $C_{18}H_{19}NO_3$: C, 72·7; H, 6·4; N, 4·7%), $\lambda_{max.}$ 224, 250 (infl.), 262, 270, 298, $\lambda_{min.}$ 241, 268, 281 mμ (log ε 4·54, 3·90, 4·00, 3·98, 3·90, 3·85, 3·97, 3·65 respectively) in EtOH.

1-Cyclohexylmethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (XII).—(a) *From the dihydroisoquinoline* (VIII). Potassium borohydride (99 mg.) was added to a solution of the dihydroisoquinoline (VIII) in methanol (10 ml.) and after the mixture had been heated on the steam bath for 1 hr. the methanol was evaporated. The residue was acidified with 2N-hydrochloric acid, and the solution was then made strongly alkaline and extracted with ether to yield a gum. A solution of this in ethanol was treated with an excess of oxalic acid, and the precipitated *tetrahydroisoquinoline hydrogen oxalate* (as XII) was recrystallised from ethanol (121 mg.), then having m. p. 196—197° (decomp.) (Found: C, 63·0; H, 7·7; N, 3·8. $C_{20}H_{29}NO_6$ requires C, 63·3; H, 7·7; N, 3·7%).

(b) *From the isoquinolinium salt* (IX; $X^- = Cl^-$).—A solution of the iodide (IX; $X^- = I^-$) (0·5 g.) in 1 : 1 aqueous ethanol was shaken for 2 hr. with freshly precipitated silver chloride (1 g.) and then filtered. Hydrated sodium acetate (0·41 g.) was added to the filtrate which was then shaken with hydrogen and 10% palladised charcoal (0·2 g.); uptake (1·9 mol.) was complete in 45 min. After removal of the catalyst, the solution was freed from alcohol by evaporation, basified, and extracted with ether, to give a base (215 mg.) which was converted in ethanol almost quantitatively into the hydrogen oxalate, m. p. and mixed m. p. with product from (a) 194—195° (decomp.).

1-Cyclohexylmethyl-6,7-dimethoxyisoquinoline (XIII).—The dihydroisoquinoline (VIII) (1·69 g.) was heated at 170° (bath) for 30 min. with 10% palladised charcoal (0·4 g.) in a stream of carbon dioxide. A solution of the products in ethanol was filtered and evaporated to dryness; crystallisation of the residue from ether and aqueous ethanol gave the *isoquinoline* (XIII) (1·16 g.), m. p. 102·5—103·5° (Found: C, 75·4; H, 8·05. $C_{18}H_{23}NO_2$ requires C, 75·75; H, 8·1%).

6,7-Dimethoxyisoquinoline-1-carboxylic Acid (XV).—1-Methyl-6,7-dimethoxyisoquinoline [10] (1 g.) was heated under reflux with benzaldehyde (8 ml.) and zinc chloride (0·6 g.) for 5 hr. at 170—180° (bath). The cooled mixture was partitioned between an excess of 2N-hydrochloric acid and benzene (30 ml.), and the separated aqueous layer, containing much crystalline matter in suspension, was basified. Extraction with ethyl acetate yielded crude 6,7-dimethoxy-1-styrylisoquinoline (1·06 g.) which was crystallised from aqueous ethanol. The crystals (750 mg.) were dissolved in 1 : 1 aqueous acetone (130 ml.) and the solution was stirred at 0—5° whilst a solution of potassium permanganate (1·31 g.) in water was added during 0·5 hr. After

* Professor Sugasawa has kindly informed us that he and Mr. H. Itoh have found *N*-benzylcoryaldine to be dimorphic, having the less stable form as prisms, m. p. 89—90°, and the more stable form as needles, m. p. 101—102°. The latter sample is identical with our material (mixed m. p. and infrared spectrum).

[19] Itoh and Sugasawa, *Tetrahedron*, 1957, **1**, 45.

the mixture had been stirred at room temperature for 1 hr., it was filtered, evaporated to 40 ml., and extracted with ethyl acetate (2 × 25 ml.). The aqueous solution was adjusted to pH 4·5 with hydrochloric acid, and the crystals of the acid (XV), m. p. 204—205° (decomp., gas), which separated at 4° overnight were collected (453 mg.). Carr and Pyman [9] record m. p. 208° (corr.).

The acid (15 mg.) was heated at 220° until gas evolution ceased; the resulting gum was converted into the picrate in ethanol. Recrystallisation from ethanol gave 6,7-dimethoxyisoquinoline picrate, m. p. and mixed m. p. 228—229° (decomp.). Carr and Pyman [9] record m. p. 227°(corr.).

β,3,4-*Trimethoxyphenethylamine* (XVII).—This has been prepared previously [20] by reduction of 2-(3,4-dimethoxyphenyl)-2-methoxynitroethane [20] with sodium amalgam. The preparation was simplified by reducing the nitro-compound in the standard way [21] with lithium aluminium hydride in anhydrous ether under reflux.

3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-[N-β,3,4-*trimethoxyphenethylcarbamoyl*)-*methyl*]*benzo*[a]*quinolizine* (XVIII).—A solution of the ester [11] (XVI; R = Et) (12·1 g.) in ethanol (20 ml.) was heated under reflux for 1·5 hr. with N-sodium hydroxide (45 ml.), then just acidified with concentrated hydrochloric acid and evaporated to dryness. After the residue had been dried for 10 min. at 90°/0·2 mm. it was exhaustively extracted with hot, dry methanol, and the solution was evaporated to dryness. Anhydrous dimethylformamide (30 ml.) was added and the solution was stirred at −2° while triethylamine (9·35 ml.) and ethyl chloroformate (3·2 ml.) were added during 10 min. The mixture was then stirred for 15 min. more before β,3,4-trimethoxyphenethylamine [20] (XVII) in dimethylformamide (20 ml.) was added dropwise in 20 min., and the stirring was continued for 1 hr. at 0° and 1 hr. at room temperature. The residue left on evaporation of the solution was dissolved in 0·5N-hydrochloric acid (200 ml.), and the solution was extracted with ethyl acetate (2 × 100 ml.), then basified (sodium carbonate) and re-extracted with ethyl acetate (1 × 200; 2 × 100 ml.). The combined ethyl acetate solutions were shaken with buffer (2 × 300 ml.) made from 0·5M-K_2HPO_4 (47 vol.) and 0·5M-KH_2PO_4 (53 vol.). Evaporation of the dried organic solution left a resin (8·82 g.) which crystallised from ethyl acetate to give the *amide* (XVIII) (2·66 g.), m. p. 176—178° raised to 179—180° by recrystallisation from ethyl acetate and from ethanol (Found: C, 68·1; H, 8·0; N, 5·5. OMe, 29·1. $C_{30}H_{42}N_2O_6$ requires C, 68·4; H, 8·0; N, 5·3; OMe, 29·45%)

The mother liquors from the above crop of amide were evaporated to dryness, and the residue in benzene was run on a column of alumina (Peter Spence; Type " H "; 40 cm. × 2·5 cm.). Elution with benzene (600 ml.) removed a syrup (1·9 g.), and 2 : 1 : 1 benzene–chloroform–ether (1 l.) eluted the crude amide (XVIII). Crystallisation of this total fraction gave the amide (1·77 g.), m. p. 177—178°; the mother liquors (A) from this fraction were reserved. Total yield of one diastereoisomer of amide (XVIII) was 4·43 g.

(±)-*Emetamine* (I).—Phosphoryl chloride (9 ml.) was added to a solution of the amide (XVIII) (77 mg.) in anhydrous xylene (25 ml.) at room temperature. The temperature of the solution was then raised to 130° during 1 hr. and maintained at 130° for 1 hr. After most of the volatile material had been evaporated, the residue was partitioned between ether (20 ml.) and 0·1N-hydrochloric acid (20 ml.), and the clear aqueous layer was extracted with more ether (2 × 10 ml.). Basification of the aqueous layer with sodium carbonate and extraction with 3 : 1 ether–chloroform (3 × 20 ml.) removed the organic bases which were recovered as a gum (67 mg.) from the dried solution by evaporation. The gum was purified on alumina (Peter Spence; Type " H "); elution with 1 : 1 benzene–chloroform removed the required base which was converted into (±)-*emetamine hydrogen oxalate* (69 mg.), m. p. 168—169° (decomp.), by treatment with an excess of hydrated oxalic acid in ethanol (Found: C, 57·4; H, 6·2. $C_{33}H_{40}N_2O_{12},2H_2O$ requires C, 57·2; H, 6·4%).

The hydrogen oxalate was dissolved in water, and the solution basified and extracted with 3 : 1 ether–chloroform to give (±)-*emetamine* (45 mg.) which, crystallised thrice from ether, had m. p. 132—133° (Found: C, 73·1; H, 7·9; N, 6·0. $C_{29}H_{36}N_2O_4$ requires C, 73·1; H, 7·6; N, 5·9%). The infrared spectrum of this product ($CHCl_3$ solution) was identical with that of natural emetamine.

When the amorphous material (1·18 g.) from the mother liquors A above was cyclised in a similar way, a mixture of basic products was obtained which was fractionated on alumina as

[20] Rosenmund, *Ber.*, 1913, **46**, 1034.
[21] Cf., *e.g.*, Hamlin and Weston, *J. Amer. Chem. Soc.*, 1949, **71**, 2210.

above. The emetamine fraction afforded (±)-emetamine hydrogen oxalate (0·23 g.), m. p. and mixed m. p. with above product 168—169° (decomp.).

2-Carbamoylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[a]*quinolizine* (XXI).—(a) *As by-product from the ring closure.* A solution of the amide (XVIII) (0·74 g.) in anhydrous xylene (30 ml.) was heated under reflux for 1 hr. with phosphoryl chloride. The mixture was worked up for base as in the foregoing experiment and yielded a gum (0·72 g.). A solution of this in benzene was run on alumina and, after development with benzene, the column was eluted with 1 : 1 benzene–chloroform to give a fraction containing (±)-emetamine [387 mg., yielding 217 mg. of (±)-emetamine hydrogen oxalate], a mixed fraction (112 mg.), and then the *amide* (XXI) (0·1 g.) which recrystallised from ethanol as needles, m. p. 226—227° after change of form at 205—210° (Found: C, 69·0; H, 8·5; N, 8·0; OMe, 18·6. $C_{19}H_{28}N_2O_3$ requires C, 68·65; H, 8·5; N, 8·4; OMe, 18·7%).

(b) *By synthesis.* The ester (XVI; R = Et) (0·5 g.) was converted into the mixed anhydride (XVI; R = CO_2Et) by the method used for the preparation of the amide (XVIII) above. Aqueous ammonia (*d* 0·880) (0·5 ml.) was added dropwise to the solution at −2° and the stirring was continued for 1 hr. at 0° and 1 hr. at room temperature. The mixture was then worked up for weak bases as for (XVIII), yielding a gum (73 mg.) which crystallised from ethanol to give the amide (XXI), m. p. and mixed m. p. with product from (a) 226—227° after change of form at 205—210°. The infrared spectra of the two samples were identical.

3-Ethyl-1,2,3,4,6,7-hexahydro-2-[(N-2-3′-indolylethylcarbamoyl)methyl]-9,10-dimethoxybenzo[a]*quinolizine* (XXII).—The ester (XVI; R = Et) (1·3 g.) was converted into the dry hydrochloride of the corresponding amino-acid as described for the preparation of the amide (XVIII). This solid was stirred at −5° with chloroform (30 ml.) and triethylamine (1·0 ml.). Ethyl chloroformate (0·35 ml.) was then added to the solution and after 25 min. finely powdered tryptamine (0·58 g.) was added. The mixture was stirred for 3 hr. and during this period was allowed to warm to room temperature, then shaken with benzene (70 ml.) and chloroform (40 ml.); the organic solution was washed with dilute sodium carbonate solution, water, and 0·5M-phosphate buffer (pH 6·6; 3 × 40 ml.). Evaporation of the dried organic solution left a resin (1·24 g.) which crystallised from benzene. Filtration of a solution of the crystals in chloroform through alumina (5 g.) and crystallisation of the product from benzene gave the *amide* (XXII) (637 mg.), m. p. 175—176° (Found: C, 73·6; H, 8·05; N, 8·7. $C_{29}H_{37}N_3O_3$ requires C, 73·2; H, 7·85; N, 8·85%).

2-(3,4-Dihydro-β-carbolin-1-ylmethyl)-3-ethyl-1,2,3,4,6,7-hexahydro]-9,10-dimethoxybenzo[a]*-quinolizine* (XXIII).—A solution of the foregoing amide (0·4 g.) in toluene (30 ml.) was heated under reflux with phosphoryl chloride (0·8 ml.) for 2·5 hr. Water (250 ml.) was added to the cooled mixture, and the clear aqueous solution was extracted with ether (2 × 100 ml.), basified, and re-extracted with ether (3 × 100 ml.). Evaporation of the dried second set of ether extracts left a solid which was chromatographed on alumina in chloroform. Recrystallisation of the purified material from ether and aqueous methanol gave the *benzoquinolizidine* (XXIII) (310 mg.), m. p. 133—134°, which underwent ready oxidation in light and air to a red product. This probably accounts for the slightly low carbon value (Found: C, 75·35; H, 7·7. $C_{29}H_{35}N_3O_2$ requires C, 76·1; H, 7·7%).

A portion was converted into the *hydrogen oxalate* by treatment with an excess of hydrated oxalic acid in ethanol; the salt recrystallised from ethanol as yellow needles, m. p. 221—225° (decomp.) (Found: C, 60·9; H, 6·1. $C_{33}H_{39}N_3O_{10},H_2O$ requires C, 60·5; H, 6·3%).

3-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-β-carbolin-1-ylmethyl)-benzo[a]*quinolizine* (XXV).—A solution of the foregoing base (131 mg.) in ethanol (10 ml.) and concentrated hydrochloric acid (2 drops) was shaken with Adams platinum oxide (15 mg.) at room temperature and pressure. Uptake (1·04 mol.) was complete in 3 hr. After the solution had been filtered, it was evaporated to dryness and the residue was crystallised from 2N-hydrochloric acid to give the *tetrahydro-β-carboline hydrochloride* (50 mg.), m. p. 227—229°, which was recrystallised from the same solvent (Found: C, 63·1; H, 7·6. $C_{29}H_{39}N_3Cl_2O_2,H_2O$ requires C, 63·3; H, 7·5%).

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