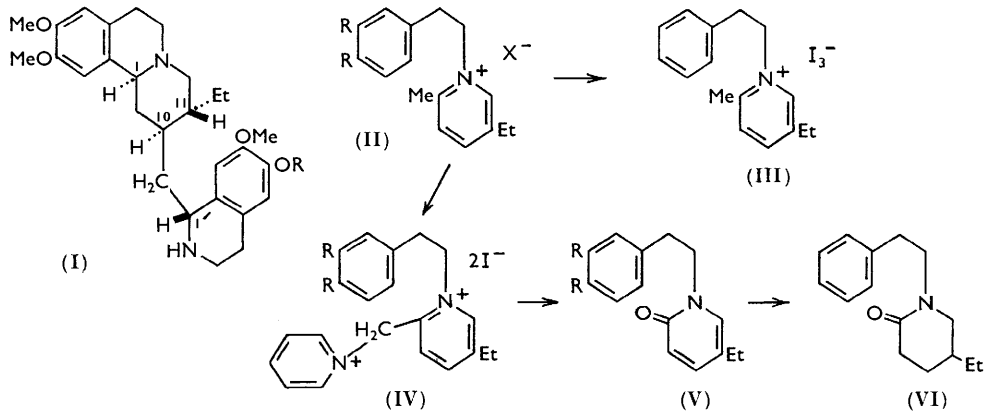
149. *Ipecacuanha Alkaloids. Part V.* Stereospecific Synthesis of (+)-O-Methylpsychotrine and (−)-Emetine.*

By A. R. Battersby and J. C. Turner.

A synthetic route to *O*-methylpsychotrine and emetine has been devised which allows controlled introduction of the asymmetric centres. The synthetic products have been resolved and shown to be identical with the natural alkaloids.

The elucidation [1] of the gross structure of emetine (I; R = Me) in 1949 stimulated considerable interest [2,3,4] in the synthesis of this alkaloid. At the time of these synthetic studies, the stereochemistry of the four asymmetric centres in emetine was unknown; (±)-emetine could thus be any one of the eight possible racemic forms of the gross structure (I; R = Me). The different routes used by Evstigneeva, Preobrashenski, *et al.*,[3] and by Barash and Osbond,[4,5] both gave mixtures of isomers, all eight being isolated by the former workers and six by the latter; one of the isomers in each case was shown to be (±)-emetine by resolution and comparison of the product with natural emetine. Very recently, van Tamelen and his co-workers [6] have confirmed that (±)-emetine is one product of the synthesis used by the Russian group.



Since the early synthetic work, studies carried out in this Laboratory [7] and elsewhere [5,6,8,9] have firmly established that the stereochemistry about the benzoquinolizidine system of emetine is that shown in structure (I; R = Me). This knowledge allows a stereospecific synthesis to be designed.

The first target in the route selected was the 5,6-dihydropyridone (XI) which we hoped to prepare by partial reduction of the corresponding pyridone (V; R = OMe). Such a

* Part IV, *J.*, 1959, 3512.

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

[2] Battersby and Openshaw, *Experientia*, 1950, **6**, 387; Battersby, Openshaw, and Wood, *J.*, 1953, 2463; Pailer and Beier, *Monatsh.*, 1957, **88**, 830; Ban, *Pharm. Bull. (Japan)*, 1955, **3**, 53.

[3] Reviewed by Evstigneeva and Preobrashenski, *Tetrahedron*, 1958, **4** 223; cf. Evstigneeva, Glushkov, and Preobrashenski, *Zhur. obshchei Khim.*, 1958, **28**, 2463.

[4] Barash and Osbond, *Chem. and Ind.*, 1958, 490

[5] Osbond, *ibid.*, 1959, 257.

[6] van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1957, **79**, 4817; van Tamelen and Hester, *ibid.*, 1959, **81**, 507.

[7] Battersby, Binks, Davidson, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982; Battersby and Cox, *ibid.*, p. 983; Battersby, *ibid.*, 1958, 1324; Battersby, Binks, and Davidson, *J.*, 1959, 2704; Battersby and Garratt, *J.*, 1959, 3512; *Proc. Chem. Soc.*, 1959, 86.

[8] Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *Chem. and Ind.*, 1958, 491.

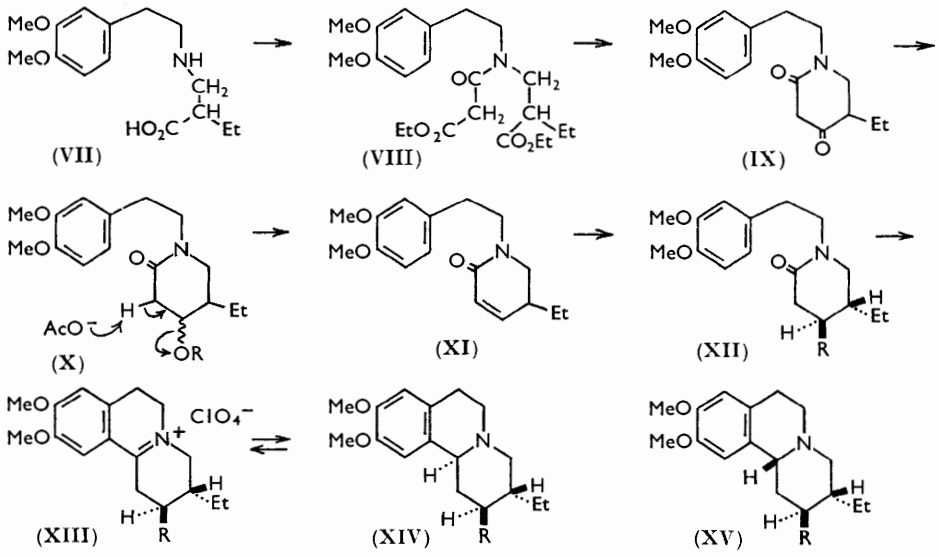
[9] Ban, Terashima, and Yonemitsu, *ibid.*, 1959, 568, 569.

partial reduction has previously been achieved[10] by the action of lithium aluminium hydride on a complex pyridone derivative related to strychnine.

Pilot experiments were carried out on the pyridone (V; R = H) prepared by Berson and Cohen's method[11] from the quaternary salt (II; R = H, X = I). Their procedure involves treatment of the latter with iodine and pyridine to yield the bis-quaternary salt (IV; R = H) which then undergoes base-catalysed cleavage to the pyridone (V; R = H). In our hands, the iodine–pyridine reaction under various conditions yielded a mixture of approximately equal quantities of the bis-quaternary salt (IV; R = H) and a salt $C_{16}H_{20}NI_3$ to which we assign the structure (III). In keeping with this structure, the latter salt was converted by aqueous sodium thiosulphate into the starting material (II; R = H, X = I). Moreover, when equimolar amounts of the iodide (II; R = H, X = I) and iodine were mixed in ethanol, an almost quantitative yield of the tri-iodide (III) separated.

Lithium aluminium hydride in refluxing ether left the pyridone (V; R = H) unchanged whereas catalytic hydrogenation, despite variations in catalyst, solvent, and acidity of the reducing medium, always yielded the corresponding piperidone (VI). In addition, Berson and Cohen's method applied to the conversion of the salt (II; R = OMe) into the methoxylated pyridone (V; R = OMe), which is the one required for the emetine synthesis, yielded only tars; we therefore turned to a different approach.

The successful route to the dihydropyridone (XI) made use of the dioxopiperidine (IX) which is readily available by Ban's synthesis.[2] In our repetition of this work, the Dieck-



mann cyclisation of the diester (VIII) has been simplified and the intermediate amino-acid (VII) obtained crystalline. Catalytic hydrogenation of the dioxopiperidine (IX) or reduction of this material with sodium borohydride gave a neutral product showing only amide-carbonyl absorption in the infrared spectrum ($\nu_{max.}$ 1642 cm.$^{-1}$); this material thus has the gross structure (X; R = H) and is probably a mixture of the two epimeric alcohols. The total product was acetylated and the ester (X; R = Ac) so obtained smoothly underwent β-elimination, when it was heated with sodium acetate, to give the required dihydropyridone (XI) [$\nu_{max.}$ 1667 cm.$^{-1}$ (>CO) and 1613 cm.$^{-1}$ (>C=C<)]. This slight raising of

[10] Woodward, Cava, Ollis, Hunger, Daeniker, and Schenker, *J. Amer. Chem. Soc.*, 1954, **76**, 4749.
[11] Berson and Cohen, *ibid.*, 1956, **78**, 416.

the carbonyl frequency by conjugation with a double bond, as opposed to the more usual lowering, has been observed previously [12] in six-membered unsaturated lactams. Further support for this structure was obtained by catalytic hydrogenation of the dihydropyridone; this gave an amorphous product having infrared absorption in the carbonyl region corresponding only to a saturated six-membered lactam ($\nu_{max.}$ 1640 cm.$^{-1}$).

The next stage in the synthesis sets up the two asymmetric centres which eventually become positions 10 and 11 of emetine, and the need for a *trans*-arrangement here led to a study of the Michael addition of malonate anion to the dihydropyridone (XI). Apparently, this has no previous analogies. However, because of the reversible nature of the Michael reaction, the product of a successful addition is normally the thermodynamically more stable one. For example,[13] the addition of malonate anion to 4-phenylcyclohex-2-enone gives *trans*-4-phenyl-3-dialkoxycarbonylmethylcyclohexanone. By analogy the major product from the Michael reaction on the dihydropyridone (XI) would be expected to be the *trans*-diester [XII; R = $CH(CO_2Et)_2$]. In fact, the acidic fraction resulting from mild hydrolysis of the total Michael product yielded 76% of a crystalline acid showing that satisfactory steric control had been achieved; this product is assigned the *trans*-structure [XII; R = $CH(CO_2H)_2$] on the above basis and further evidence for this stereochemistry is adduced below.

Decarboxylation of the acid [XII; R = $CH(CO_2H)_2$] yielded the *trans*-oxopiperidinylacetic acid (XII; R = $CH_2{\cdot}CO_2H$) which as the ester (XII; R = $CH_2{\cdot}CO_2Et$) was cyclised by phosphoryl chloride in high yield. The product was best isolated as the perchlorate (XIII) since the corresponding free iso-base was very unstable. It thus remained to reduce this product to the tricyclic compound (XIV; R = $CH_2{\cdot}CO_2Et$) in order to afford the correct intermediate for the synthesis of emetine. There were strong indications that catalytic hydrogenation of the salt (XIII) would be controlled to give the base (XIV; R = $CH_2{\cdot}CO_2Et$) rather than the isomer (XV; $CH_2{\cdot}CO_2Et$) as it was known [6,7] that hydrogenation of (XIII; R = Et) affords a high yield of the base (XIV; R = Et). However, because of the importance of this hydrogenation step, a further check was carried out. The optically active ester (XIV; R = $CH_2{\cdot}CO_2Me$) of proven stereochemistry was available from the work of Battersby and Harper [14] on protoemetine (XIV; R = $CH_2{\cdot}CHO$); when the former was dehydrogenated with mercuric acetate, the dehydro-derivative (XIII; R = $CH_2{\cdot}CO_2Me$) was isolated as the crystalline perchlorate. Catalytic hydrogenation of this product afforded the starting material (XIV; R = $CH_2{\cdot}CO_2Me$) in good yield, which confirms that the desired stereochemistry is set up in the hydrogenation step. Thus the product obtained in 90% yield by hydrogenation of the synthetic material (XIII; R = $CH_2{\cdot}CO_2Et$) is the base (XIV; R = $CH_2{\cdot}CO_2Et$) and its infrared spectrum in solution was identical with that of the optically active ester (XIV; R = $CH_2{\cdot}CO_2Et$) derived [14] from protoemetine.

In preliminary work, the crude malonic ester [XII; R = $CH(CO_2Et)_2$] was cyclised by phosphoryl chloride to the salt [XIII; R = $CH(CO_2Et)_2$] which as in the cases above gave mainly one isomer on catalytic hydrogenation; this isomer is assigned the structure [XIV; R = $CH(CO_2Et)_2$] by analogy with the foregoing results.

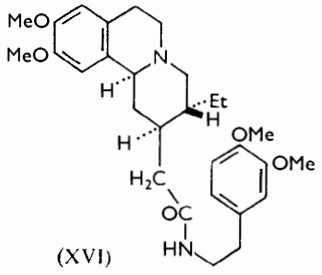
The remaining stages to (±)-*O*-methylpsychotrine (XVII; R = Me) were based upon the work of Battersby and Harper [14] who used the optically active acid (XIV; R = $CH_2{\cdot}CO_2H$) prepared from protoemetine. In the present studies, the preparation of the amide (XVI) was improved in yield and in ease of operation by treating 3,4-dimethoxyphenethylamine with the mixed anhydride (XIV; R = $CH_2{\cdot}CO{\cdot}O{\cdot}CO_2Et$) prepared from the triethylamine salt of the acid (XIV; R = $CH_2{\cdot}CO_2H$) and ethyl chloroformate. The (±)-amide (XVI) so obtained had infrared absorption in solution identical with that of the optically active partially synthetic amide (XVI) prepared earlier.[14]

[12] Edwards and Singh, *Canad. J. Chem.*, 1954, **32**, 683.
[13] Bergmann and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1953, **75**, 3226.
[14] Battersby and Harper, *J.*, 1959, 1748.

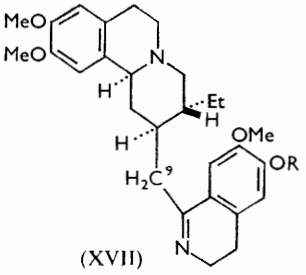
Cyclisation of the amide (XVI) with phosphoryl chloride gave 80% of (±)-*O*-methylpsychotrine (XVII; R = Me) which was proved to be structurally identical with the natural alkaloid by infrared measurements in solution. The (±)-base was resolved as its dibenzoyltartrate and the (+)-base so obtained was identical with natural *O*-methylpsychotrine (XVII; R = Me).

This stereospecific synthesis also constitutes a formal synthesis of the minor Ipecacuanha alkaloids cephæline (I; R = H) and psychotrine (XVII; R = H) since these bases have been prepared earlier [15] from (+)-*O*-methylpsychotrine.

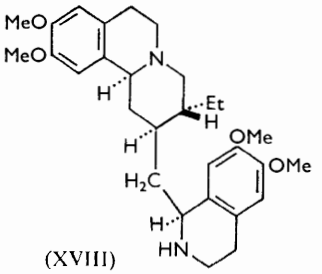
Hydrogenation of (+)-*O*-methylpsychotrine hydrogen oxalate is known [16] to give almost entirely isoemetine (XVIII), and models show that the conformation of the *O*-methylpsychotrine molecule which puts the greatest distance between the two positively charged nitrogen atoms is shaped like a partly opened hinge having $C_{(9)}$ as the back about which the hinge opens. Hydrogenation should thus occur most readily on the outside of the hinge and the models show that this leads to isoemetine. If this interpretation is correct, it follows that the restraining positive charges should be removed in order to increase the yield of emetine (I; R = Me) from the hydrogenation step. Accordingly, synthetic (+)-*O*-methylpsychotrine free base was hydrogenated in ethanol to give 55% of (−)-emetine (I; R = Me), isolated as the hydrobromide. This product was proved to be identical with the natural alkaloid by a rigorous comparison (p. 725); also, crystalline *N*-benzoylemetine was prepared from the synthetic and the natural material, and the two samples were identical.



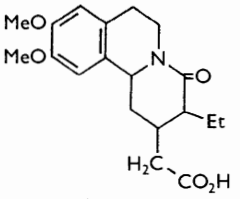
(XVI)



(XVII)



(XVIII)



(XIX)

The mother-liquors from the separation of synthetic (−)-emetine hydrobromide contained (−)-isoemetine (XVIII) which was isolated as its characteristic *N*-benzoyl derivative. Again this was proved to be identical with authentic *N*-benzoylisoemetine prepared from natural *O*-methylpsychotrine.

After the preliminary publication of this synthesis,[17] Burgstahler and Bithos [18] briefly reported a new synthesis of the gross structure (XIX) which gave a mixture of three isomers. One of these was shown to have the required stereochemistry for use as an

[15] Carr and Pyman, *J.*, 1914, **105**, 1591; Brindley and Pyman, *J.*, 1927, 1067.
[16] Karrer, Eugster, and Ruttner, *Helv. Chim. Acta*, 1948, **31**, 1219.
[17] Battersby and Turner, *Chem. and Ind.*, 1958, 1324.
[18] Burgstahler and Bithos, *J. Amer. Chem. Soc.*, 1959, **81**, 503.

intermediate in the synthesis of emetine by reducing it to the alcohol (XIV; R = $CH_2 \cdot CH_2 \cdot OH$). We were glad to establish that this alcohol sent to us by Professor Burgstahler was identical with the product obtained by reducing our preparation of the ester (XIV; R = $CH_2 \cdot CO_2Et$) with lithium aluminium hydride.

Experimental

For general directions, see Part I.[19]

5-Ethyl-2-methyl-1-phenethylpyridinium Bromide (II; R = H, X = Br) *and Iodide* (II; R = H, X = I).—Phenethyl bromide (100 g.) was heated at 105° with 5-ethyl-2-methylpyridine (66 g.) for 2 hr. and the mixture was then cooled to give a solid. This was dissolved in the minimum volume of ethanol and treated with light petroleum (b. p. 40—60°) to incipient turbidity; crystals separated (115 g.), having m. p. 176—177°. Part was recrystallised thrice from ethanol–acetone to give the *pyridinium bromide*, m. p. 178—179° (Found: C, 63·15; H, 6·8; N, 4·4. $C_{16}H_{20}NBr$ requires C, 62·75; H, 6·6; N, 4·55%).

A solution of the foregoing bromide (25 g.) in hot water (20 ml.) was treated with potassium iodide (30 g.) in water (10 ml.). The precipitated iodide was collected, washed with a small volume of water, then with ethanol, and recrystallised from ethanol to give the *pyridinium iodide* (23·1 g.), m. p. 178—180° raised to 182—183° by three recrystallisations from ethanol (Found, in material dried at 56°: C, 54·3; H, 5·8; N, 3·6. $C_{16}H_{20}NI$ requires C, 54·4; H, 5·7; N, 3·95%).

5-Ethyl-2-methyl-1-phenethylpyridinium Tri-iodide (III).—A solution of the foregoing pyridinium iodide (1·54 g.) in pyridine (15 ml.) was heated on the steam-bath with iodine (1·13 g.) for 4 hr. under nitrogen. After cooling, the crystalline precipitate was collected, washed with pyridine, then with ether, and dried (1·63 g.). The filtrate was evaporated nearly to dryness and the residue was extracted with cold water (3 × 20 ml.). To the aqueous solution was added the above crystalline product, and cold 2N-sodium hydroxide was run in until no further blood-red colour was formed. This solution was then continuously extracted with light petroleum (b. p. 40—60°) for 24 hr. to yield, on evaporation of the petroleum, a gum (497 mg.) which crystallised. Four recrystallisations from light petroleum (b. p. 40—60°) gave 5-ethyl-1-phenethyl-2-pyridone (V; R = H) (334 mg.), m. p. 56—57°; Berson and Cohen [11] record m. p. 56—57°.

The water-insoluble fraction above crystallised from ethanol to give *5-ethyl-2-methyl-1-phenethylpyridinium tri-iodide* (III) as brown needles (503 mg.), m. p. 96—98° raised to 99—100° by recrystallisation twice from ethanol (Found, in material dried at 80°: C, 32·15; H, 3·0; N, 2·15; I, 62·45. $C_{16}H_{20}NI_3$ requires C, 31·65; H, 3·3; N, 2·3; I, 62·7%).

The tri-iodide (0·4 g.) in chloroform (10 ml.) was shaken with a solution of sodium thiosulphate (0·33 g.) in water (15 ml.); the chloroform solution was immediately decolorised. Evaporation of the chloroform left a solid which in a small volume of water was treated with an excess of potassium iodide. The precipitated solid (50 mg.) was recrystallised twice from acetone, to give the pyridinium iodide, m. p. and mixed m. p. 180—182°.

When solutions of iodine (222 mg.) in ethanol (5 ml.) and the pyridinium iodide (II; R = H, X = I) (308 mg.) in ethanol (10 ml.) were mixed at 0°, the pyridinium tri-iodide (III) immediately crystallised (495 mg.), m. p. and mixed m. p. with above product 99—100°.

5-Ethyl-1-phenethyl-2-oxopiperidine (VI).—A solution of the pyridone (V; R = H) (22·4 mg.) in ethanol (10 ml.) was shaken with hydrogen and platinum (10 mg.) at room temperature and pressure; uptake (2 mol.) ceased after 2 hr. After the solution had been filtered, it was evaporated to leave a gum which distilled in a short-path still at 130—140° (bath)/1 mm. to give *5-ethyl-1-phenethyl-2-oxopiperidine* (VI) (Found, in freshly distilled material: C, 78·0; H, 9·5. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·15%).

α-(*3,4-Dimethoxyphenethylaminomethyl*)*butyric Acid* (VII).—This *amino-acid*, prepared by Ban's method [2] and crystallised from ethanol, had m. p. 160—161° (Found: C, 63·5; H, 8·2; N, 4·9. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·4; N, 5·0%).

1-(*3,4-Dimethoxyphenethyl*)-*5-ethyl-2,4-dioxopiperidine* (IX).—The foregoing amino-acid

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

was converted into the ethyl ester as usual [2] and the product (60 g.) was stirred vigorously in benzene (400 ml.) with 10% aqueous sodium hydrogen carbonate (600 ml.). A solution of ethoxycarbonylacetyl chloride (41 g.) in benzene (100 ml.) was added dropwise and the stirring was continued for 15 min. after the addition was complete. The benzene solution was separated and shaken with an excess of N-hydrochloric acid and then with water. Evaporation of the dried benzene solution left a gum (85 g.) which was dissolved in anhydrous toluene (1 l.) and part of the toluene (50 ml.) was distilled off in an apparatus protected against moisture. Sodium ethoxide (4·8 g. of sodium in 100 ml. of ethanol) was then added dropwise to the boiling toluene solution during 1 hr. and the heating was adjusted so that ethanol and toluene continuously distilled. The slow distillation was continued for a further hour and the mixture of toluene and the sodium salt of the product, which was a thick gum, was then cooled. The sodium salt was worked up as described by Ban [2] to give the dioxopiperidine (IX) (53·7 g.). Part was converted as usual into the phenylhydrazone, m. p. 168—169° (Ban [2] records m. p. 169°) (Found: C, 69·5; H, 7·6; N, 10·5. Calc. for $C_{23}H_{29}O_3N_3$: C, 69·8; H, 7·4; N, 10·6%).

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-4-*hydroxy*-2-*oxopiperidines* (X; R = H).—(a) *Catalytic reduction.* A solution of the foregoing dioxopiperidine (1·46 g.) in ethanol (150 ml.) was shaken with hydrogen and Adams catalyst (0·29 g.) at room temperature and pressure; uptake (1 mol.) ceased after 7 hr. The catalyst was filtered off and the solution evaporated to give a gum (1·47 g.). Part was distilled at 140° (bath)/10^{-5} mm. to give the (? mixed) *hydroxyoxopiperidines* (X; R = H) (Found: C, 66·1; H, 8·4; N, 4·2. $C_{17}H_{25}O_4N$ requires C, 66·4; H, 8·2; N, 4·5%).

(b) *Borohydride reduction.* Sodium borohydride (6·9 g.) was added portionwise in 30 min. to a solution of the foregoing dioxopiperidine (53 g.) in ethanol (500 ml.). The solution was then heated under reflux for 15 min. and the ethanol was evaporated. After addition of water, sufficient dilute hydrochloric acid was added to give a neutral suspension. This was extracted with chloroform (3 × 200 ml.), and the combined extracts were washed with water, dried, and evaporated to give a gum (53·6 g.) which in chloroform solution had infrared absorption identical with that shown by the product from (a) above.

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-5,6-*dihydropyrid*-2-*one* (XI).—The foregoing alcohol(s) (4·84 g.) was heated under reflux for 14 hr. with acetic anhydride (40 ml.) and finely powdered anhydrous sodium acetate (10 g.). The excess of anhydride was evaporated at atmospheric pressure and the residue was heated at 150° (bath) for 5 min. Fresh acetic anhydride (10 ml.) was added and the mixture was heated under reflux for 2 hr.; the anhydride was then removed and the residue heated as above. Aqueous 0·4N-ammonia (50 ml.) was added and the mixture was extracted with ether (4 × 50 ml.). After the ethereal solution had been washed with 5% aqueous potassium carbonate (2 × 20 ml.) and water (3 × 20 ml.), it was dried and evaporated to leave a gum (3·95 g.). Part was distilled at 120° (bath)/10^{-2} mm. in a short-path still to give the *dihydropyrid*-2-*one* (XI) (Found: C, 70·15; H, 8·2. $C_{17}H_{23}O_3N$ requires C, 70·55; H, 8·0%).

trans-1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-2-*oxo*-4-*piperidinylmalonic Acid* [XII; R = $CH(CO_2H)_2$].—The above dihydropyridone (3·95 g.) in anhydrous ethanol (20 ml.) was added dropwise in 0·5 hr. to a boiling solution of diethyl malonate (4 g.) and sodium ethoxide (0·25 g.) in anhydrous ethanol (60 ml.); the solution was then heated under reflux for 8 hr. After addition of glacial acetic acid (0·5 ml.), the solution was evaporated to *ca.* 20 ml. and diluted with water (20 ml.). The resultant suspension was extracted with ether (3 × 100 ml.), and the extracts were washed with 5% aqueous sodium carbonate (2 × 20 ml.) and water (3 × 20 ml.), dried, and evaporated. The resultant oil was freed from diethyl malonate by heating it at 90°/0·1 mm. for 1 hr. A gum *A* (5 g.) remained which was heated in 0·3N-aqueous-ethanolic sodium hydroxide (50 ml.; 66% of ethanol) at 50° for 20 hr. The solution was evaporated to 20 ml. and, after addition of water (10 ml.), was extracted with ether; this removed the oily neutral fraction (1·14 g.). After the aqueous solution had been acidified, it was extracted with chloroform (4 × 100 ml.); the combined organic extracts were washed with water (3 × 20 ml.), dried, and evaporated to yield the acidic fraction (2·83 g.) as a resin. This crystallised from 50% aqueous acetone (30 ml.) to give the *malonic acid* [XII; R = $CH(CO_2H)_2$] (2·15 g.), m. p. 151·5—152·5° (decomp.) (Found: C, 61·5; H, 7·1; N, 3·5. $C_{20}H_{27}O_7N$ requires C, 61·1; H, 6·9; N, 3·5%).

2-*Diethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* [XIII; R = $CH(CO_2Et)_2$].—The crude product (481 mg.) from the Michael reaction, gum *A* above, was heated in anhydrous toluene (4 ml.) for 1 hr. under reflux with phosphoryl

chloride (0·5 ml.); after the mixture had been cooled, it was extracted with water (3 × 10 ml.). The aqueous solution was washed with ether (2 × 10 ml.), basified to pH 10 with potassium carbonate, and extracted quickly with ether (4 × 15 ml.). Without delay, the ethereal solution was then extracted with 0·3N-hydrochloric acid (5 × 1 ml.), and perchloric acid was added dropwise to the combined acid extracts until no further precipitate was formed. The crystalline solid was collected (0·1 g.) and recrystallised from ethyl acetate, to give the *benzo*[a]*quinolizinium perchlorate* (72 mg.), m. p. 140—140·5° (Found: C, 54·6; H, 6·8; N, 2·6. $C_{24}H_{34}O_{10}NCl$ requires C, 54·2; H, 6·4; N, 2·6%).

2-*Diethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,5,6,7,11b-*octahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* [as XIV; R = $CH(CO_2Et)_2$].—The foregoing perchlorate (60 mg.) in 50% aqueous ethanol (10 ml.) was shaken with hydrogen and platinum at room temperature and pressure; uptake (1 mol.) was complete in 15 min. The catalyst was filtered off, the ethanol was evaporated, and the residue crystallised from ethyl acetate to give the *quinolizinium perchlorate* (36 mg.), m. p. 187° (Found: C, 54·0; H, 6·9. $C_{24}H_{36}O_{10}NCl$ requires C, 54·0; H, 6·8%).

trans-1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-2-*oxo*-4-*piperidinylacetic Acid* (XII; R = $CH_2{\cdot}CO_2H$). The corresponding malonic acid [XII; R = $CH(CO_2H)_2$] (145 mg.) was heated under reflux for 7 hr. with 60% acetic acid (10 ml.). The solvent was evaporated and the resulting resin was crystallised from aqueous acetone to give the *acetic acid* (0·1 g.), m. p. 153—153·5°, depressed to 138—142° on admixture with the starting material (Found: C, 65·1; H, 7·5; N, 4·2. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* (XIII; R = $CH_2{\cdot}CO_2Et$).—A solution of the foregoing acid (7·37 g.) in anhydrous ethanol (160 ml.) containing concentrated sulphuric acid (5·8 ml.) was heated under reflux for 8 hr. Part (120 ml.) of the ethanol was then distilled off and the residue was poured into an excess of aqueous sodium carbonate at 0°. Ether-extraction afforded the ester (XII; R = $CH_2{\cdot}CO_2Et$) as a clear gum (7·8 g.). A solution of part (3·23 g.) of this in anhydrous toluene (60 ml.) was heated under reflux for 30 min. with freshly distilled phosphorus oxychloride (2·6 ml.). The mixture was then worked up as described for the analogue [XIII; R = $CH(CO_2Et)_2$] to give a crystalline perchlorate. Recrystallisation from ethanol gave the *quinolizinium perchlorate* (3·42 g.), m. p. 113—114° (Found: C, 55·1; H, 6·5; N, 3·1. $C_{21}H_{30}O_8NCl$ requires C, 54·8; H, 6·6; N, 3·05%), $\lambda_{max.}$ 246, 304, 354, $\lambda_{min.}$ 227, 265, 322 mμ (log ε 4·21, 3·96, 4·03, 3·74, 2·79, 3·75 respectively) in EtOH.

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,5,6,7,11b-*octahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* (as XIV; R = $CH_2{\cdot}CO_2Et$).—A solution of the foregoing perchlorate (7·51 g.) in aqueous ethanol (300 ml.) containing 10% of water was shaken with hydrogen and Adams catalyst (0·14 g.) at room temperature and pressure; uptake (1·0 mol.) was complete in 15 min. Removal of the catalyst and solvent followed by crystallisation of the residue from ethanol gave the *dimethoxybenzo*[a]*quinolizinium perchlorate* (as XIV; R = $CH_2{\cdot}CO_2Et$) as needles (6·73 g.), m. p. 145—146·5° (Found: C, 54·8; H, 6·9; N, 2·9. $C_{21}H_{32}O_8NCl$ requires C, 54·6; H, 7·0; N, 3·0%).

This product (2·91 g.) was dissolved in the minimum volume of cold water and the solution was basified with potassium carbonate. Ether-extraction (4 × 100 ml.) afforded as usual the free dimethoxybenzo[*a*]quinolizine base (2·27 g.) which when crystallised from light petroleum (b. p. 40—60°) had m. p. 66—66·5°. Part of this was converted in ethanol into the *picrate* which after recrystallisation from ethanol had m. p. 165—166° (Found: C, 54·7; H, 5·8; N, 9·7. $C_{27}H_{34}O_{10}N_4$ requires C, 54·9; H, 5·8; N, 9·5%).

3-*Ethyl*-1,2,3,4,5,6,7,11b-*octahydro*-2-2′-*hydroxyethyl*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* (as XIV; R = $CH_2{\cdot}CH_2{\cdot}OH$).—A solution of the foregoing base (XIV; R = $CH_2{\cdot}CO_2Et$) (99 mg.) in anhydrous ether (120 ml.) was heated under reflux for 12 hr. with lithium aluminium hydride (0·5 g.). The excess of hydride was decomposed with water, and the mixture was then treated with 50% aqueous potassium hydroxide to dissolve the inorganic precipitate. After separation of the ether, the aqueous solution was extracted with more ether (3 × 50 ml.), and the combined ethereal solutions were washed with water and extracted with N-sulphuric acid (10 ml.). The acidic solution was basified with sodium hydroxide and extracted with ether (3 × 100 ml.), to give a gum (85 mg.) which was converted into the perchlorate in ethanol. Recrystallisation from water and then absolute ethanol–ethyl acetate gave the *hydroxyethylquinolizinium perchlorate* (85 mg.), m. p. 178—181° after slight softening at 175° (corr.) (Found, in material dried at 65°: C, 54·6; H, 7·3; N, 3·3. $C_{19}H_{30}O_7NCl$ requires C, 54·4; H, 7·2; N, 3·3%).

Dehydrogenation of (−)-3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*methoxycarbonylmethylbenzo*[a]*quinolizine* (XIV; R = $CH_2 \cdot CO_2Me$) *by Mercuric Acetate and Hydrogenation of the Product.*—To a solution of this base [19] (59 mg.) in aqueous acetic acid (1·5 ml.; 10% of acetic acid by vol.) was added mercuric acetate (170 mg.) and potassium acetate (10 mg.), and the solution was then heated under reflux for 50 min. After the cooled solution had been filtered and the pad washed with water and methanol, the filtrate was saturated with hydrogen sulphide. The precipitated sulphides were filtered off (" Filtercel ") and the filtrate was evaporated to *ca.* 3 ml.; addition of a few drops of 60% perchloric acid precipitated crystals (55 mg.). These recrystallised from methanol–ether to give the quinolizinium perchlorate (XIII; R = $CH_2 \cdot CO_2Me$) (44 mg.), m. p. 110—111°, $\lambda_{max.}$ 246, 303, 353, $\lambda_{min.}$ 226, 265, 321 mμ (log ε 4·17, 3·94, 4·10, 3·51, 2·72, 3·57 respectively) in EtOH.

This product (41·2 mg.) in methanol (15 ml.) was shaken with hydrogen and platinum (15 mg.) at room temperature and pressure; uptake (1·04 mol.) was complete in 8 min. After removal of the catalyst and solvent, the residue was crystallised from ethyl acetate to give the perchlorate of the base (XIV; R = $CH_2 \cdot CO_2Me$) (29 mg.), m. p. 144—146°. The base (21 mg.) was recovered from this salt as usual and it crystallised from light petroleum (b. p. 60—80°) as needles, m. p. and mixed m. p. 98—100°, $[\alpha]_D^{20}$ −34·6° ± 0·8° (*c* 1·56 in methanol), infrared spectrum identical with that of the starting material. The latter showed $[\alpha]_D^{20}$ −35·4° ± 0·8° (*c* 2·82 in methanol).

2-[(N-3′,4′-*Dimethoxyphenethylcarbamoyl*)*methyl*]-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizine* (XVI).—The ester (XIV; R = $CH_2 \cdot CO_2Et$) (4·05 g.) was heated under reflux for 5 hr. with 0·5N-aqueous-ethanolic sodium hydroxide (90 ml.; 50% of water); N-hydrochloric acid (50 ml.) was then added and the solution was evaporated to dryness. The residue was dried at 90°/0·05 mm. and then dissolved in dry dimethylformamide (80 ml.) containing triethylamine (2·5 ml.). This stirred solution was cooled to −5° and treated dropwise during 1 min. with freshly distilled ethoxycarbonyl chloride (2 ml.). After the stirring had been continued for 25 min., 3,4-dimethoxyphenethylamine (9 ml.) was added dropwise in 1 min. and the mixture was stirred at −5° to 0° for 1 hr. and then at room temperature overnight. Evaporation of the solvents left a residue which was partitioned between ethyl acetate and dilute hydrochloric acid; the ethyl acetate was separated and extracted with more dilute hydrochloric acid. The combined acid solutions were extracted twice with ethyl acetate, and the organic solution was rejected. After basification of the aqueous solution with potassium carbonate, it was extracted thrice with ethyl acetate. The latter extracts (total 400 ml.) were shaken with aqueous buffer (1 × 200 ml.; 1 × 150 ml.) made from 0·5M-KH_2PO_4 (11 vol.) and 0·5MK_2HPO_4 (2 vol.), and the combined aqueous extracts were shaken thrice with ethyl acetate (total 300 ml.). Evaporation of the combined solutions in ethyl acetate left a crystalline mass (4·16 g.) which was recrystallised from ethyl acetate and from aqueous ethanol, to give the *amide* (XVI) as needles (3·98 g.), m. p. 146—148° (Found: C, 70·2; H, 8·1; N, 5·5. $C_{29}H_{40}O_5N_2$ requires C, 70·1; H, 8·1; N, 5·6%).

(±)-O-*Methylpsychotrine* (XVII; R = Me).—The foregoing amide (1·98 g.) in anhydrous toluene (130 ml.) was heated under reflux for 1·5 hr. with freshly distilled phosphoryl chloride (3 ml.). The cooled mixture was worked up as in the cases above, to yield an ethereal solution of the basic products which was dried and evaporated to a gum (1·8 g.). A solution of this base in ethanol (60 ml.) was treated with hydrated oxalic acid (1 g.) to afford (±)-O-*methylpsychotrine hydrogen oxalate* (2·23 g.), m. p. 162—163° (decomp.) dependent on the rate of heating (Found: C, 56·9; H, 6·5. $C_{33}H_{46}O_{12}N_2,2H_2O$ requires C, 57·0; H, 6·7%).

The base was recovered from the hydrogen oxalate by means of ether, from which it was recovered by evaporation as a gum which crystallised from anhydrous ether to give (±)-O-*methylpsychotrine* as prisms, m. p. 110—112° (Found, in material dried at 78°: C, 73·0; H, 8·0. $C_{29}H_{38}O_4N_2$ requires C, 72·8; H, 8·0%).

Synthetic (+)-O-*Methylpsychotrine* (XVII; R = Me).—The base, recovered as above from the (±)-*O*-methylpsychotrine hydrogen oxalate (2·23 g.), was dissolved in methanol (39 ml.) and treated with (−)-*OO*-dibenzoyltartaric acid (1·245 g.). The mixture was warmed just sufficiently to give a clear solution and then was treated with ether (20 ml.). Crystallisation was initiated by seeding with (+)-*O*-methylpsychotrine dibenzoyltartrate prepared from the natural alkaloid; the crystals (1·33 g.) recrystallised readily from methanol–ether. The base was recovered in ether as usual from this salt (366 mg.) and, after removal of the ether, the residue crystallised from anhydrous ether, to give synthetic (+)-O-*methylpsychotrine* (0·2 g.),

m. p. 122—123·5° unchanged on admixture with the natural alkaloid of same m. p. The synthetic and the natural base had identical infrared spectra and *X*-ray powder photographs. The synthetic base showed $[\alpha]_D^{25}$ +42·8° ± 0·5° (*c* 1·87 in EtOH), the natural base $[\alpha]_D^{25}$ +42·3° ± 0·5° (*c* 1·87 in EtOH).

Synthetic (−)-*Emetine* (I; R = Me).—A solution of the foregoing base (0·45 g.) in ethanol (20 ml.) was hydrogenated over Adams catalyst (0·1 g.) at 21°/752 mm.; uptake (1·02 mol.) ceased after 15 min. After the catalyst had been filtered off, N-hydrochloric acid (3 ml.) was added to the filtrate which was evaporated to dryness. A solution of the residue in water (5 ml.) was adjusted to pH 2·5 with aqueous ammonia and then ammonium bromide (0·45 g.) was added. The crystals which slowly separated were collected, washed with dilute hydrobromic acid (2 × 0·5 ml.), and dried over potassium hydroxide pellets, to give synthetic (−)-emetine hydrobromide (354 mg. containing 7% of H_2O). This salt was recrystallised from dilute hydrobromic acid (4 ml. of water containing 4 drops of 48% hydrobromic acid), to give needles (293 mg.), m. p. 243—245° after sintering 238°, unchanged on admixture with the hydrobromide of natural emetine of same m. p.

The synthetic (−)-*emetine* base was isolated from the hydrobromide in ether as usual and was recovered by evaporation; it had $[\alpha]_D^{23}$ −49·5° ± 1·0° (*c* 2·06) and natural emetine had $[\alpha]_D^{23}$ −49·2° ± 1·0° (*c* 3·56; both in $CHCl_3$). The infrared spectra of the synthetic and the natural alkaloid (in $CHCl_3$) were identical.

Part (125 mg.) of the (−)-emetine was converted into synthetic N-*benzoylemetine* by Carr and Pyman's method;[15] the product (129 mg.) had m. p. 183—184° unchanged on admixture with *N*-benzoylemetine of the same m. p. prepared from natural emetine. Synthetic material had $[\alpha]_D^{20}$ −63·7° ± 1·0° (*c* 2·09 in $CHCl_3$); authentic *N*-benzoylemetine had $[\alpha]_D^{20}$ −63·7° ± 1·0° (*c* 2·06 in $CHCl_3$). The two samples of *N*-benzoylemetine had identical infrared spectra and *X*-ray powder photographs.

Synthetic (+)-N-*Benzoylisoemetine*.—The solution remaining after removal of the synthetic emetine hydrobromide above was basified with sodium hydroxide and extracted with ether (3 × 50 ml.); the combined ethereal solutions were washed with water, dried, and evaporated to yield a resin (221 mg.). This was benzoylated by Carr and Pyman's method,[15] and the resinous product (291 mg.) was crystallised from methanol–ether, to give synthetic N-*benzoylisoemetine* (180 mg.), m. p. 201·5—203° unchanged on admixture with authentic material of the same m. p. (Found: C, 74·8; H, 7·5; N, 4·8. $C_{36}H_{44}O_5N_2$ requires C, 74·5; H, 7·6; N, 4·8%). Synthetic material had $[\alpha]_D^{20}$ +47·9° ± 1·0° (*c* 2·72); authentic *N*-benzoylisoemetine had $[\alpha]_D^{20}$ +48·0° ± 1·0° (*c* 2·32, both in $CHCl_3$). The two samples of *N*-benzoylisoemetine had identical infrared spectra and *X*-ray powder photographs.

Grateful acknowledgment is made to Dr. D. Traill and Imperial Chemical Industries Limited for the gift of 5-ethyl-2-methylpyridine, to Professor A. W. Burgstahler for the analysis of compound (XIV; R = $CH_2 \cdot CH_2 \cdot OH$), and to Whiffen and Sons Limited for financial support.

THE UNIVERSITY, BRISTOL. [*Received, July 23rd*, 1959.]