432. *Chemical Constitution and Amœbicidal Action. Part III.* Synthesis of an Analogue of Emetine and Two Stereoisomers of De-ethylemetine.*

By M. Barash and J. M. Osbond.

An open chain analogue (VI) of emetine has been prepared as a potential amœbicide. A new route to de-ethylemetine (XV) has also been developed which has allowed the synthesis of two stereoisomers of this base.

Although challenged by antibiotics and a range of relatively simple compounds effective in varying degrees, emetine [1] (VII) is still [2] pre-eminent in the treatment of amœbiasis.[3] Many attempts to obtain simple analogues having the same or enhanced activity have so far not had practical success: [4] it appears that emetine is very specific. So we decided to prepare a close analogue, (VI), formally derived from emetine (VII) by fission of the bonds *a*–*a* and *b*–*b* and then to utilise one of the intermediates, (II), for synthesis of de-ethylemetine (XV).

The starting material, 3 : 4-dimethoxyphenethyl iodide, was prepared from 3 : 4-dimethoxybenzyl cyanide, obtained by chloromethylation of veratrole [5] or from veratraldehyde. Catalytic reduction of the aldehyde gave 3 : 4-dimethoxyphenethyl alcohol which was converted into the chloride and nitrile; the derived ethyl ester was reduced by lithium aluminium hydride to 3 : 4-dimethoxyphenethyl alcohol. Alternatively veratraldehdye was condensed with ethyl chloroacetate (Darzens reaction) to give ethyl 3 : 4-dimethoxyphenylglycidate; [6] alkaline hydrolysis gave the sodium salt, which with aqueous oxalic acid gave 3 : 4-dimethoxyphenylacetaldehyde [8] whence lithium aluminium hydride

* Part II, *J.*, 1952, 4785.

[1] See Janot, in Manske and Holmes's "The Alkaloids," Academic Press Inc., New York, 1953, Vol. III, p. 363.

[2] Rogers, *Brit. Med. J.*, 1912, I, 1424; 1912, II, 405.

[3] Woodruff, *Practitioner*, 1954, **173**, 441; "Treatment of Human Amœbiasis," *Trans. Roy. Soc. Trop. Med. Hyg.*, 1956, **50**, 109.

[4] Osbond, *J.*, 1951, 3461; Amin, Linnell, and Sharp, *J. Pharm. Pharmacol.*, 1957, **9**, 588.

[5] Bide and Wilkinson, *J. Soc. Chem. Ind.*, 1945, 84; Gaivron, *J. Amer. Chem. Soc.*, 1949, **71**, 744.

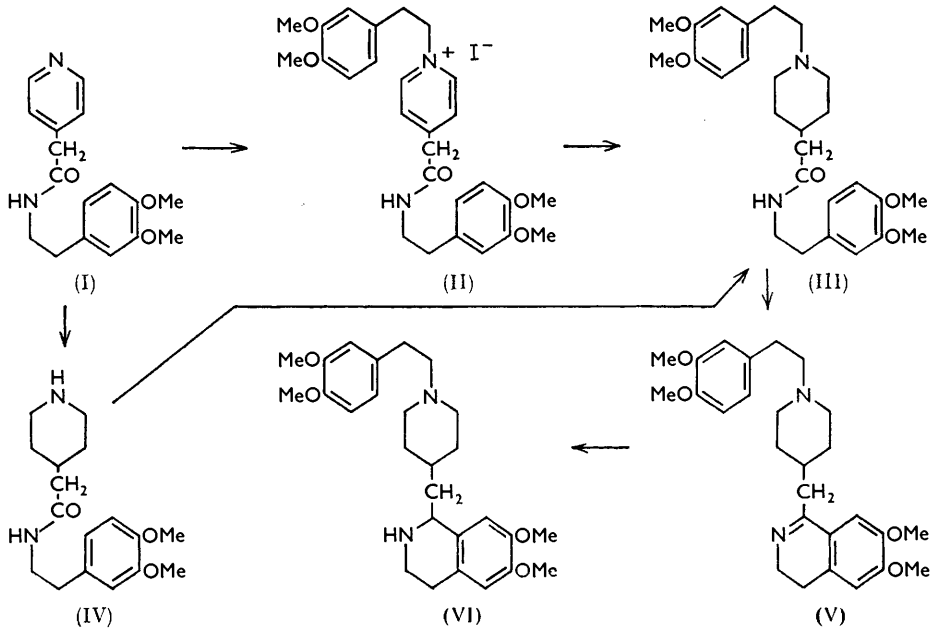
[6] Cf. Henecka, *Annalen*, 1953, **583**, 126.

[7] Cf. Loftfield, *J. Amer. Chem. Soc.*, 1950, **72**, 2499; Shinya, *J. Agric. Chem. Soc. Japan*, 1950, **24**, 281; *Chem. Abs.*, 1953, **47**, 6374.

[8] Eliel, McBride, and Kaufmann, *J. Amer. Chem. Soc.*, 1953, **75**, 4293.

afforded the alcohol. The alcohol with thionyl chloride gave 3 : 4-dimethoxyphenethyl chloride and thence the iodide.

The other starting material, ethyl 4-pyridylacetate, was prepared either from 4-acetylpyridine [9] or from 4-vinylpyridine by the Kindler modification of the Willgerodt reaction [10] to give 4-4′-pyridyl(thioacetyl)morpholine (with some 4-ethylpyridine [11] and thioacetomorpholide). Alkaline hydrolysis of the morpholide gave the required acid which was



esterified without isolation. Condensing ethyl 4-pyridylacetate with 3 : 4-dimethoxyphenethylamine gave the amide (I). Quaternisation of this with 3 : 4-dimethoxyphenethyl iodide in methanol gave the iodide (II), but reaction in benzene or without solvent gave a non-crystalline product having part of its iodine in non-ionic form.[12] The quaternary salt was reduced catalytically to the piperidine base (III). This base was also prepared by the route (I) ⟶ (IV) ⟶ (III), which confirms its structure. In a third attempt quaternisation of the 3 : 4-dimethoxyphenethyl iodide and ethyl 4-pyridylacetate and reduction of the quaternary salt to ethyl 1-(3 : 4-dimethoxyphenethyl)-4-piperidylacetate was successful, but the final step, condensation with the phenethylamine, gave no crystalline product.

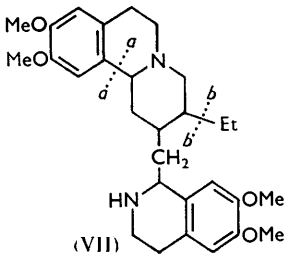
The base (III) was readily cyclised by phosphorus pentachloride in chloroform or by phosphorus oxychloride in toluene to the dihydro*iso*quinoline (V), hydrogenation of which gave the required tetrahydro*iso*quinoline (VI).

Although de-ethylemetine * (XV) has already been prepared four times,[13] it has not been evaluated for amœbicidal properties and only one stereoisomer has been isolated. The base (XV) contains three asymmetric centres, so four racemic stereoisomers are possible and might have interesting chemotherapeutic properties.

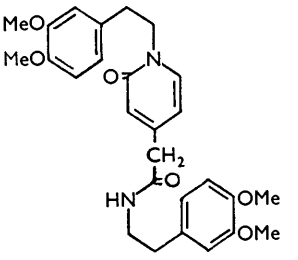
* The name bisnoremetine, previously used, is ambiguous as it could apply to emetine with 2OH replacing 2OMe. Ed.

[9] Malan and Dean, *J. Amer. Chem. Soc.*, 1947, **69**, 1797; Katritzky, *J.*, 1955, 2586.
[10] Noller and Wunderlich, *J. Amer. Chem. Soc.*, 1952, **74**, 3835.
[11] Cf. Fieser and Kilmer, *ibid.*, 1940, **62**, 1354.
[12] Cf. Hartwell and Kornberg, *ibid.*, 1946, **68**, 868; Kosower, *ibid.*, 1955, **77**, 3883.
[13] (*a*) Pailer, Schneglberger, and Reifschneider, *Monatsh.*, 1952, **83**, 513; (*b*) Pailer and Strohmayer, *ibid.*, 1952, **83**, 1198; (*c*) Tomimatsu, *J. Pharm. Soc. Japan*, 1953, **73**, 75; (*d*) Sugasawa and Oka, *Pharm. Bull.* (*Japan*), 1954, **2**, 85.

We first tried to oxidise the quaternary salt (II) by the well-known alkaline ferricyanide procedure [14] to the pyridone (VIII) which could by obvious methods be converted into de-ethylemetine (XV), but obtained only tars; there was a similar result in experiments with the simpler 1-(3 : 4-dimethoxyphenethyl)-4-picolinium iodide. Since



(VII)



(VIII)

this oxidation can be carried out with the 3-methylpyridinium salt [15] but not with the 2-methyl isomer [16] it appears that the reactive 2- or 4-methylene group is further oxidised possibly in the anhydro-base form. The pyridone (VIII) was later prepared by a different method [13d] and converted into de-ethylemetine.

Our second approach is shown in formulæ (IX) ⟶ (XV); we had in mind its adaptation to the synthesis of emetine. 4-Methyl-2-pyridone [16] with 3 : 4-dimethoxyphenethyl iodide in aqueous *tert.*-butyl alcohol containing potassium hydroxide gave the *N*-substituted pyridone (IX); although under alkaline conditions the *N*-alkylpyridone is normally obtained, there are several recorded cases [17] where *O*-alkylation is the chief reaction; so, to confirm the structure of our compound, 2-bromo-4-methylpyridine [18] was converted by 3 : 4-dimethoxyphenethyl iodide into a (non-crystalline) salt (XVII) which on mild alkaline hydrolysis [19] gave the identical pyridone (IX).

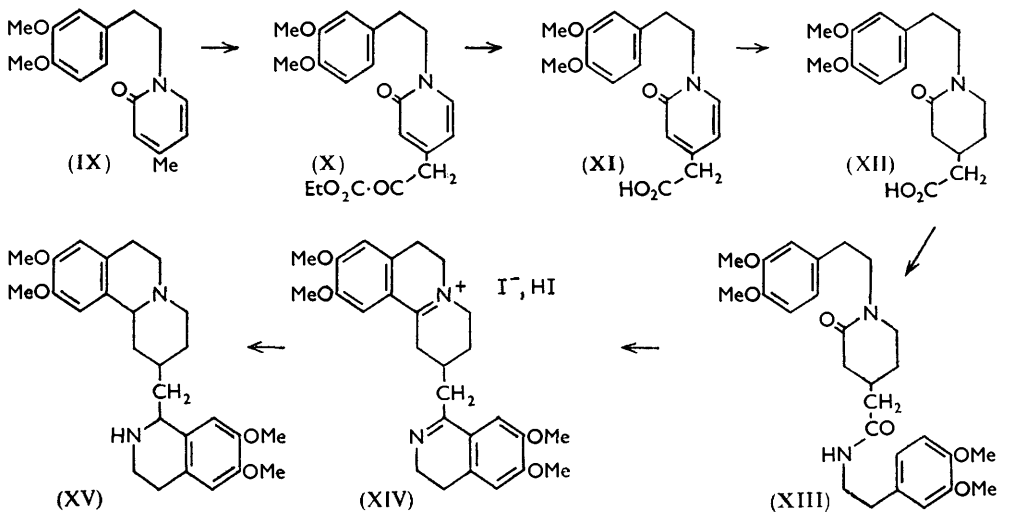
This pyridone with ethyl oxalate in the presence of potassium ethoxide [16,17,20] gave the pyruvate ester (X). Attempts to oxidise the pyruvate ester or its potassio-derivative by alkali and hydrogen peroxide together [16] were unsuccessful. It was necessary first to hydrolyse the ester with dilute alkali at 0° and then to add hydrogen peroxide which gave a good yield of the pyridone-acid (XI); a more convenient route was to use the potassio-derivative of the ester (X) in this reaction. From the mother-liquor of the oxidation a small amount of the 4-methyl-2-pyridone (IX) was isolated, presumably as a result of a reverse Claisen reaction.

The structure of the acid (XI) was proved in two ways. The ester (X) or its potassio-derivative with hydroxylamine hydrochloride gave the hydroxyimino-ester (XVIII), hydrolysed by alkali to the acid (XIX), which afforded the nitrile (XX) by pyrolysis or, preferably, on treatment with acetic anhydride.[21] Hydrolysis of the nitrile (XX) with dilute alkali yielded the acid (XI). Secondly, the acid (XI) at its decomposition point lost carbon dioxide and gave the 4-methyl-2-pyridone (IX); this behaviour is typical of 2- and 4-pyridylacetic acids and would be expected with a similar 2-pyridone-acid. The methyl ester of acid (XI) was prepared both from this acid by diazomethane or from the nitrile (XX) by methanolic hydrogen chloride. The piperidone-acid (XII) was obtained by catalytic reduction of the pyridone-acid by using Adams catalyst. The structure of the acid (XII) was proved by cyclising its methyl ester (XXI) in toluene with

[14] Thyagarajan, *Chem. Rev.*, 1958, **58**, 439; Sugasawa, Kodama, and Inagaki, *Ber.*, 1941, **74**, *B*, 455.
[15] Bradlow and VanderWerf, *J. Org. Chem.*, 1951, **16**, 73.
[16] Adams and Schrecker, *J. Amer. Chem. Soc.*, 1949, **71**, 1186.
[17] Leonard and Boyer, *ibid.*, 1950, **72**, 2980; Ramirez and Paul, *J. Org. Chem.*, 1954, **19**, 183.
[18] Lott and Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 70.
[19] Cf. VanderWerf and Bradlow, *J. Org. Chem.*, 1951, **16**, 1143.
[20] Kaslon and Cook, *J. Amer. Chem. Soc.*, 1945, **67**, 1969; Wislicenus, *Ber.*, 1909, **42**, 1141; Borsche and Manteuffel, *Annalen*, 1938, **526**, 22; Snyder and Williams, *J. Amer. Chem. Soc.*, 1954, **76**, 1298.
[21] Cf. Barnard and Bateman, *J.*, 1950, 926.

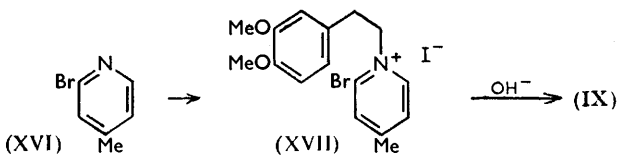
phosphorus oxychloride to the known 1 : 2 : 3 : 4 : 6 : 7-hexahydrobenzo[*a*]quinolizinium iodide [13b] (XXII), and the properties of the salt (XXII) agreed with those in the literature.

The triethylammonium salt of the 2-oxo-4-piperidylacetic acid (XII) in dimethylformamide with ethyl chloroformate gave, in the usual way,[22] the ethoxycarbonyloxy-derivative, which without isolation was treated with 3 : 4-dimethoxyphenethylamine in the



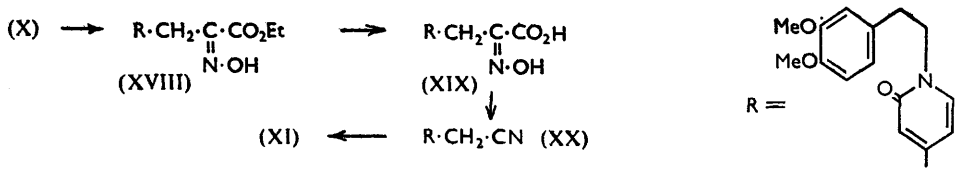
presence of triethylamine to give the amide (XIII) in two crystalline forms, m. p. 120—121° and m. p. 130—131°, which were interconvertible. This amide had previously been prepared by Tomitsu [13b] as a gum and, after our work was complete, Sugasawa and Oka [13d] reported it as having m. p. 130—131°.

Phosphorus oxychloride in toluene effected double ring closure of the amine (XIII) to the quaternary compound, characterised as the iodide hydriodide (XIV) and bromide



hydrobromide, both crystalline; the ultraviolet absorption spectrum was in agreement with this structure.

Catalytic reduction of the iodide hydriodide was slow but complete, and the first racemate of de-ethylemetine (XV; A) separated as a crystalline dihydriodide and afforded

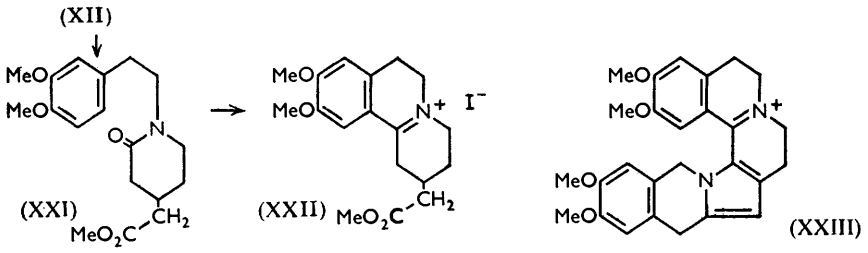


a dihydrobromide and dihydrogen dioxalate. The mother-liquors yielded a second isomer (XV; B), isolated as dihydrogen dioxalate and dihydrobromide. The structures of the

[22] Vaughan and Osato, *J. Amer. Chem. Soc.*, 1952, **74**, 676; Boissonnas, *Helv. Chim. Acta*, 1951, **34**, 874.

isomers were confirmed by the ultraviolet spectrum and dehydrogenation by mercuric acetate [23] of isomer B to de-ethylrubremetinium bromide (XXIII) as an orange-scarlet solid in good yield; it had the characteristic ultraviolet absorption [13b] (cf. rubremetinium bromide [24]).

Amœbicidal evaluation of these compounds was carried out on weanling rats infected with *E. histolytica*, by a modification of Jones's method.[25] Under standard conditions emetine has CD_{50} of 6·25—12·5 mg./kg.; by contrast, suitable hydrohalide salts of bases (V), (VI), (XIV), and (XV, A and B) were inactive at 250, 500, 5 × 100, 5 × 100, and 5 × 100 mg./kg., respectively.



Experimental

3 : 4-*Dimethoxybenzyl Alcohol*.—Veratraldehyde (120 g.; m. p. 43·5—45°) was hydrogenated in methanol in the presence of Raney nickel (*ca.* 10 g. in methanol) at 90° with an initial pressure of 50 atm., substantially completely in 2 hr. The mixture was cooled, filtered, and concentrated to a viscous oil which on distillation gave the alcohol (116 g., 95·5%), b. p. 112—120°/0·25—0·35 mm., n_D^{19} 1·5520.

3 : 4-*Dimethoxyphenylacetonitrile*.[27]—Thionyl chloride (17 c.c.) was added in 25 min. to 3 : 4-dimethoxybenzyl alcohol (25 g.) in benzene (20 c.c.) at 0°. After the initial reaction had subsided the benzene and thionyl chloride were removed under reduced pressure on the water-bath. The residue was refluxed in benzene (*ca.* 100 c.c.) with potassium cyanide (14·6 g.) in water (50 c.c.) for 2¾ hr. with stirring. The phases were separated and the aqueous phase was re-extracted with benzene. The benzene extracts were dried and distilled. The residue was distilled to give the nitrile (16·7 g., 63%), b. p. 128—130°/0·1—0·25 mm., m. p. 60—61°.

Ethyl 3 : 4-*Dimethoxyphenylacetate*.—A solution of the above nitrile [5] (90 g.) in dry ethanol (500 c.c.) was saturated with hydrogen chloride, then cooled to 0°. The nitrile which separated gradually redissolved to give a purple solution. The mixture was kept at 0° overnight, then most of the alcohol was removed under reduced pressure at 35°. Dry ether was added to the residue and the crystalline *ethyl* 3 : 4-*dimethoxyphenylacetimidoate hydrochloride* was collected and washed with dry ether; it recrystallised from cold ethanol–ether in prisms, m. p. 114·5—115° (Found: N, 5·7; Cl, 13·4. $C_{12}H_{18}O_3NCl$ requires N, 5·4; Cl, 13·7%). The salt was dissolved in water; after a few minutes at room temperature an oil separated and this was extracted with ether. The aqueous solution was then kept in contact with ether for 18 hr., the ether extracts being separated from time to time. The ether extracts were combined, washed with dilute sodium carbonate solution and with water, and dried (Na_2SO_4). The residue after removal of the ether was distilled, to give the ester (94·3 g., 83%), b. p. 132—136°/0·1—0·3 mm., n_D^{20} 1·5192 (Found: C, 64·5; H, 8·0. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

Ethyl 3 : 4-*Dimethoxyphenylglycidate*.—A mixture of 3 : 4-dimethoxybenzaldehyde (re-distilled; 66·4 g.) and ethyl chloroacetate (redistilled; 41·3 c.c.) was added during 4 hr. to a stirred solution from sodium (9·4 g.) and absolute ethanol (133·2 c.c.) at −10°. Stirring was continued for a further 6 hr. at room temperature. After being kept at room temperature

[23] Battersby and Openshaw, *J.*, 1949, 567.
[24] Karrer, Eugster, and Ruttner, *Helv. Chim. Acta*, 1948, **31**, 1219.
[25] Jones, *Ann. Trop. Med. Parasitol*, 1956, **40**, 130.
[26] Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 951.
[27] Livshits, Bainova, Bazilevskaya, Genkin, Preobrazhenskii, Rozanova, and Baranova, *Zhur. obshchei Khim.*, 1951, **21**, 1354.

overnight the mixture was poured on ice containing acetic acid (*ca.* 5 c.c.). The yellow solid was filtered and dried (P_2O_5; vac.). After several days a dry solid (81·5 g., 77·1%), m. p. 49—51°, was obtained. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *ester* as needles, m. p. 52·5—53·5° (Found: C, 62·1; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·8; H, 6·3%).

3 : 4-*Dimethoxyphenylacetaldehyde*.—The glycidic ester (12·6 g.) in ether (100 c.c.) was added in 15 min. to a solution from sodium (1·25 g.) in methanol (17 c.c.) and water (1 c.c.) at 5°. The mixture was kept at 0° for 19 hr., and ether (20 c.c.) added after 7 hr. The sodium 3 : 4-dimethoxyphenylglycidate (12·05 g., 98%) was collected and washed with ether. The salt (18·9 g.) was dissolved in water (75 c.c.) and added to oxalic acid (13·5 g.) in water (60 c.c.) at 95—100° with a rapid stream of nitrogen passing through the solution, during 15—20 min. The solution was then heated for a further 5 min., cooled, and extracted three times with chloroform. The chloroform extracts were washed with water and dried (Na_2SO_4). Distillation gave the pure aldehyde (8·6 g., 62%), b. p. 115—121°/0·7—1·0 mm., n_D^{20} 1·5430 (lit.,[28] n_D^{20} 1·5431) (Found: C, 66·3; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·7%). The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate as orange-red needles, m. p. 168—169° (lit.,[28] m. p. 169—169·5°).

3 : 4-*Dimethoxyphenethyl Alcohol*.—(1) Ethyl 3 : 4-dimethoxyphenylacetate (33·6 g.) in dry ether (150 c.c.) was added dropwise with stirring to a suspension of lithium aluminium hydride (7·5 g.) in dry ether (150 c.c.); after 0·5 hour's heating on a water-bath a fairly granular precipitate was obtained. Ethyl acetate (25 c.c.) was added, followed by 2N-sulphuric acid (excess) with ice-cooling. The aqueous phase was extracted with ether six times, the combined extracts were washed with sodium carbonate solution, dried, and evaporated. Distillation gave the alcohol (25·2 g., 92%), b. p. 126—128°/0·3—0·7 mm., m. p. 45—46·5° (lit.,[29] m. p. 48°) (Found: C, 66·4; H, 8·2. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). The *toluene*-p-*sulphonate*, prepared in pyridine at 0—5°, separated from ether–light petroleum and had m. p. 49—51·5° (1·04 g. from 1·82 g.) (Found: C, 60·9; H, 6·1; S, 9·4. $C_{17}H_{20}O_5S$ requires C, 60·7; H, 6·0; S, 9·5%).

(2) 3 : 4-Dimethoxyphenylacetaldehyde (8·63 g.) was reduced by lithium aluminium hydride (2 g.) in ether (100 c.c.), as above, to the alcohol (6·6 g., 75%), b. p. 112—118°/0·3 mm., m. p. 41—43°.

3 : 4-*Dimethoxyphenethyl Chloride*.—Thionyl chloride (8·92 g., 0·075 mole) in dry benzene (15 c.c.) was added with stirring to a solution of 3 : 4-dimethoxyphenethyl alcohol (9·1 g., 0·05 mole) and diethylaniline (7·93 c.c., 0·05 mole) in benzene (60 c.c.) during 0·5 hr. The mixture was kept at room temperature for 1·5 hr., then heated on a boiling-water bath for 10 min. Two-thirds of the benzene was removed under reduced pressure and the resulting solution was washed with water, dilute aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the chloro-compound (9·45 g., 94%), b. p. 126°/0·3 mm., laths, m. p. 37·5—39·5° [from ether–light petroleum (b. p. 40—60°) at −15°] (Found: C, 59·8; H, 6·7; Cl, 17·3. Calc. for $C_{10}H_{13}O_2Cl$: C, 59·9; H, 6·5; Cl, 17·7%).

3 : 4-*Dimethoxyphenethyl Iodide*.—(1) Sodium iodide (132 g.; dry and powdered) was refluxed in dry ethyl methyl ketone (1 l.) for 1·5 hr. The mixture was then cooled, 3 : 4-dimethoxyphenethyl chloride (117 g.) in dry ethyl methyl ketone (200 c.c.) was added, and the mixture refluxed for a further 10 hr. Precipitated sodium chloride was removed, most of the ketone was distilled off, and the residue was dissolved in ether and water. The aqueous layer was extracted six times with ether and washed with sodium thiosulphate solution and water. The ether extract was dried and evaporated and the residue distilled, to give the iodo-compound (157 g., 92%), b. p. 112°/0·3 mm., prisms, m. p. 45—47° [from ether–light petroleum (b. p. 40—60°)] (Found: I, 42·9. Calc. for $C_{10}H_{13}O_2I$: I, 43·4%).

(2) 3 : 4-Dimethoxyphenethyl toluene-*p*-sulphonate (1·68 g.) was refluxed in dry acetone (25 c.c.) with sodium iodide (0·82 g.) for 3 hr. The sodium toluene-*p*-sulphonate (0·92 g.) was filtered off and the acetone was removed under reduced pressure, and the product was obtained as in (1), having m. p. and mixed m. p. 45·5—48°.

4-4′-*Pyridyl(thioacetyl)morpholine*.—Redistilled 4-vinylpyridine (10·5 g., 0·1 mole), sulphur (4·8 g., 0·15 mole), and morpholine (13·0 g., 0·15 mole) were refluxed at 160° for 16 hr. The resultant dark mass was dissolved in ethanol (15 c.c.) and cooled to 0°. The morpholide (11·83 g., 53%) was collected and recrystallised from ethanol as yellow prisms, m. p. 105—107°

[28] Kaufmann, Eliel, and Rosenkrantz, *Ciencia* (*Mexico*), 1946, **7**, 136; Scopf, Gottman, Meisel, and Neuroth, *Annalen*, 1949, **563**, 86.

[29] Brace, *J. Amer. Chem. Soc.*, 1953, **75**, 357.

(lit.,[9] m. p. 104—105·5°). The alcoholic mother-liquor was basified with aqueous potassium hydroxide and extracted 6 times with ether. Distillation of the ether-soluble material gave 4-ethylpyridine (1·35 g.), b. p. 50°/12 mm., n_D^{20} 1·4988 (lit., 1·5022) [picrate, m. p. and mixed m. p. 167—169° (from alcohol)], and thioacetomorpholide (0·6 g.), b. p. 143—146°/12 mm., m. p. 90—92° (lit.,[29] m. p. 89—91·2°) (Found: C, 49·7; H, 7·8; N, 9·6; S, 22·1. Calc. for $C_6H_{11}ONS$: C, 49·6; H, 7·6; N, 9·6; S, 22·0%).

Ethyl 4-Pyridylacetate.—4-4′-Pyridyl(thioacetylmorpholine (33·3 g., 0·15 mole) was refluxed with potassium hydroxide (23 g.) in alcohol (180 c.c.) for 16 hr. Water (360 c.c.) was added and the solution concentrated to half-volume under reduced pressure; then water (180 c.c.) was added and the solution was evaporated nearly to dryness, made just acid with 2N-hydrochloric acid, evaporated to dryness, and co-distilled with ethanol (twice) and benzene. The dry residue was suspended in absolute ethanol (200 c.c.), saturated with hydrogen chloride without cooling, and kept overnight at room temperature. The alcohol was removed and dilute sodium carbonate and ether were added. The residue from the ether-extracts was distilled, to give the ester (18·9 g., 76%), b. p. 86—90°/0·2—0·4 mm. The *hydrochloride* separates from ethanol as prisms, m. p. 165—168° (decomp.) (Found: C, 54·0; H, 6·1; N, 6·9. $C_9H_{12}O_2NCl$ requires C, 53·7; H, 6·0; N, 6·9%).

Ethyl 1-(3 : 4-Dimethoxyphenethyl)-4-piperidylacetate.—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and ethyl 4-pyridylacetate (1·65 g.) were heated on a boiling-water bath for 2 hr., to give a quaternary salt which was hydrogenated in ethanol (60 c.c.) and triethylamine (1·6 c.c.) and at 145—150°/75 atm. for 3 hr. in the presence of Raney nickel. The product after removal of the alcohol was treated with excess of 2N-sodium carbonate, and extracted with ether three times. The extract was dried (Na_2SO_4) and distilled (b. p. 188—192°/0·6 mm.; 1·16 g.), affording the *product* which after several recrystallisations from ether–light petroleum (b. p. 40—60°) at −20° formed prisms, m. p. 38·5—40° (Found: C, 68·4; H, 8·9; N, 3·8. $C_{19}H_{29}O_4N$ requires C, 68·0; H, 8·7; N, 4·2%).

N-(3 : 4-*Dimethoxyphenethyl*)-α-4-*pyridylacetamide* (I).—3 : 4-Dimethoxyphenethylamine (9·05 g.), ethyl 4-pyridylacetate (8·25 g.), and a few drops of dry pyridine were heated at 180° for 3 hr., then dissolved in benzene from which the crude amide (11·3 g., 75%) separated. Recrystallisation from benzene gave the *amide* (10·5 g.) as needles, m. p. 93·5—95° (Found: C, 68·3; H, 7·3; N, 9·2. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%).

N-(3 : 4-*Dimethoxyphenethyl*)-α-4-*piperidylacetamide* (IV).—The foregoing amide (3 g.) was shaken in ethanol (40 c.c.) with Raney nickel for 1½ hr. The suspension was filtered and the nickel was washed with glacial acetic acid. Further acetic acid (60 c.c.) was added to the filtrate which was then hydrogenated in the presence of Adams catalyst. The product after removal of solvent was partitioned between dilute sodium carbonate and chloroform. Several chloroform extracts were obtained, washed with water, and dried (Na_2SO_4). The solid residue crystallised from benzene–light petroleum (b. p. 40—60°), to give the *amide* (1·72 g.), m. p. 93—96°, needles (Found: C, 67·0; H, 8·4; N, 8·8. $C_{17}H_{26}O_3N_2$ requires C, 66·6; H, 8·5; N, 9·1%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-[N-(3 : 4-*dimethoxyphenethyl*)*carbamoylmethyl*]*pyridinium Iodide* (II).—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and *N*-(3 : 4-dimethoxyphenethyl)-α-4-pyridylacetamide (3·0 g.) were refluxed in absolute methanol (25 c.c.) in nitrogen for 16 hr. After concentration of the solution to *ca.* 10 c.c. the quaternary salt (4·87 g.), m. p. 142—146°, slowly separated. Recrystallisation from absolute ethanol gave the *pyridinium iodide*, m. p. 146—148° (softens at 145°), as yellow prisms (Found: C, 53·4, 53·7; H, 6·0, 6·0; I′, 22·2, 22·2. $C_{27}H_{33}O_5N_2I,H_2O$ requires C, 53·1; H, 5·8; I′, 20·8%).

N-(3 : 4-*Dimethoxyphenethyl*)-α-(3 : 4-*dimethoxyphenethyl*-4-*piperidyl*)*acetamide* (III).—(1) The iodide (II) (11·85 g.) in methanol (300 c.c.) was hydrogenated at atmospheric pressure and room temperature in the presence of Adams catalyst (0·5 g.) (uptake 1560 c.c.; theor., 1555 c.c.). The solution was filtered, concentrated, and basified with 2N-sodium hydroxide, and the base extracted with chloroform (5 times). The recovered *base* (8·25 g., 88%) separated from ethyl acetate as needles, m. p. 135·5—136° (Found: C, 68·8; H, 8·0; N, 6·1. $C_{27}H_{38}O_5N_2$ requires C, 68·9; H, 8·1; N, 5·9%).

3 : 4-Dimethoxyphenethyl iodide (0·73 g.), the amide (IV), and potassium carbonate (0·52 g.) were refluxed in dry benzene (20 c.c.) for 3 hr. The solution was washed with water and evaporated. The residual solid crystallised from ethyl acetate, to give the amide (II) (0·6 g.), m. p. and mixed m. p. 133—135·5° (from ethyl acetate).

4-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)-1-(3 : 4-*dimethoxyphenethyl*)*piperidine*

(V).—(i) Phosphorus pentachloride (3 g.) was added to the amide (III) (2·46 g.) in dry chloroform (30 c.c.) at 5°. The mixture was kept at 0° for 0·5 hr. with intermittent shaking, then at room temperature for 18 hr. Most of the chloroform was removed under reduced pressure and ice and excess of 2N-sodium hydroxide were added. The basic material was extracted with chloroform, washed with water, and recovered. The residue dissolved in warm ether and after removal of some flocculent material was recovered as an oil. Dilute hydrochloric acid was added, and the yellow solution evaporated to a yellow foam. After distillation of the residue 3 times with alcohol it was dissolved in ethanol to which ether was added. The *dihydrochloride* separated as yellow prisms (2·42 g., 88%), m. p. 105—110°. Recrystallisation from ethanol–ether with a trace of dry hydrogen chloride gave pale yellow prisms which, after drying at 50—60° *in vacuo*, had m. p. ~180—185° (softening at 160°, doubtless owing to hydration). The salt was very hygroscopic and its dilute ethanolic solution had a bright blue fluorescence (Found: C, 59·9; H, 7·1; N, 5·2. $C_{27}H_{36}O_4N_2,2HCl,H_2O$ requires C, 59·7; H, 7·4; N, 5·1%).

The *dihydrobromide* was less hygroscopic and crystallised from ethanol as pale yellow prisms, m. p. (air-dried) m. p. 131—136° (meniscus and frothing at 155—160°) (Found: C, 48·1, 48·3; H, 6·2, 6·6; N, 3·9; Br, 23·9; H_2O, 10·2. $C_{27}H_{36}O_4N_2,2HBr,3H_2O$ requires C, 48·5; H, 6·6; N, 4·2; Br, 23·9; H_2O, 8·1%).

The *base*, crystallised from light petroleum (b. p. 60—80°) containing a few drops of ether, had m. p. 99—102·5° (Found: C, 71·8; H, 8·4; N, 5·8. $C_{27}H_{36}O_4N_2$ requires C, 71·6; H, 8·0; N, 6·2%).

(ii) The amide (III) (2·35 g.) was refluxed in dry toluene (15 c.c.) and phosphorus oxychloride (10 c.c.) for 1 hr., cooled, washed by decantation with light petroleum (b. p. 60—80°), and dissolved in aqueous alcohol. Excess of 50% sodium hydroxide solution was added and the basic material extracted with ether (3 times) and washed with water. The recovered base was converted into the dihydrobromide which separated from ethanol as yellow prisms (2·32 g., 75%), m. p. (air-dried) and mixed m. p. 131—136°.

1-(3 : 4-*Dimethoxyphenethyl*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)-*piperidine* (VI).—The dihydrobromide (V) (3·07 g.) was hydrogenated at room temperature and atmospheric pressure in methanol (50 c.c.) with Adams catalyst (0·2 g.). The filtered solution was concentrated to 25—30 c.c. and treated with hydrobromic acid, to give a dihydrobromide (2·55 g., 92%), m. p. 188—192°. Recrystallisation from methanol gave the *tetrahydroisoquinoline dihydrobromide* as prisms, m. p. (air-dried) 190—196° (Found: C, 50·3; H, 6·6; N, 4·5; Br, 24·2; H_2O, 5·1. $C_{27}H_{38}O_4N_2,2HBr,2H_2O$ requires C, 49·7; H, 6·80; N, 4·3; Br, 24·5; H_2O, 5·5. Found, in a sample dried at 90° *in vacuo*: loss, H_2O, 2·5; C, 51·9; H, 6·4. $C_{27}H_{38}O_4N_2,2HBr,H_2O$ requires H_2O, 2·8; C, 51·1; H, 6·7%).

In a preliminary reduction the tetrahydro*iso*quinoline was isolated as the *dihydrogen dioxalate*, needles (from methanol–ether), m. p. 173·5—175° (decomp. 180—185°) (Found: C, 58·2; H, 6·8; N, 4·7. $C_{27}H_{38}O_4N_2,2H_2C_2O_4$ requires C, 58·6; H, 6·7; N, 4·4%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-*picolinium Iodide*.—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and γ-picoline (0·93 g.) were heated on a boiling-water bath for 2 hr. The crystalline precipitate was dissolved in ethanol from which the quaternary *salt* separated as yellow needles (6·6 g.), m. p. 184—187° (Found: C, 50·2; H, 5·3; N, 3·6. $C_{16}H_{20}O_2NI$ requires C, 49·9; H, 5·2; N, 3·6%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-*methyl*-2-*pyridone Hydrochloride* (IX).—(i) To potassium hydroxide (6·6 g.), dissolved in water (3 c.c.) and *tert.*-butyl alcohol (80 c.c.), 4-methyl-2-pyridone (10·9 g., 0·1 mole) was added and the solution was heated for a few minutes to obtain complete dissolution. 3 : 4-Dimethoxyphenethyl iodide (29·2 g., 0·1 mole) was added and the solution was refluxed for 2·75 hr. The solvent was then removed and the residue was partitioned between benzene and 2N-sodium hydroxide. The aqueous layer was extracted 3 times with benzene which was then removed, and the residue was dissolved in a very small volume of ethanol and treated with excess of ether saturated with dry hydrogen chloride. The *hydrochloride* (24·45 g., 79%) recrystallised from ethanol–ether as needles, m. p. 170—172° (Found: C, 62·6; H, 6·8; N, 4·5. $C_{16}H_{19}O_3N,HCl$ requires C, 62·0; H, 6·2; N, 4·5%).

(ii) 4-Methyl-2-pyridone (5·45 g.) was warmed with a solution from potassium (1·95 g.) and *tert.*-butyl alcohol (40 c.c.) for a few minutes, 3 : 4-dimethoxyphenethyl chloride (11·1 g.) was added, the whole refluxed for 6 hr., and the product obtained as described above as the hydrochloride (11·09 g., 71·6%) m. p. 165—166°.

(iii) 3 : 4-Dimethoxyphenethyl iodide (5·84 g.) and 2-bromo-4-methylpyridine were heated

on a boiling-water bath for 5 hr. The residue was lixiviated with dry ether, dissolved in aqueous ethanol, treated with excess of 2N-sodium hydroxide at room temperature, and kept overnight. The solution was extracted with chloroform, dried, and evaporated. The residue gave on distillation a fraction (1·4 g.), b. p. 200—202°/0·5 mm., which gave the pyridone hydrochloride, m. p. 165—169°, when treated with ether saturated with dry hydrogen chloride. Recrystallisation gave the pure hydrochloride, m. p. 169—172°, identical with the compound prepared as above (Found: Cl, 11·4. $C_{16}H_{19}O_3N$,HCl requires Cl, 11·4%).

Ethyl 1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylpyruvate* (X).—Absolute ethanol (16·6 c.c.) was added to potassium (2·53 g.) under dry ether (14·4 c.c.), and dissolution completed by warming. Ethyl oxalate (9·48 g.) in ether (60 c.c.) was added dropwise at *ca.* 10°. After 10 min. 1-(3 : 4-dimethoxyphenethyl)-4-methyl-2-pyridone [from the hydrochloride (18·6 g.)] in benzene (90 c.c.) was added dropwise in 8 min. at 0°. After 2 days an oil separated which became solid on addition of ether (*ca.* 90 c.c.). This yellow potassio-derivative salt (19·0 g.) was filtered off after 4 days and washed with dry ether. From the filtrate a further 3·8 g. (total 91·2%) were obtained.

The potassio-derivative (10·3 g.) was added portionwise to 2N-sulphuric acid (32·5 c.c.), ice (17 g.) and chloroform (55 c.c.) with vigorous shaking. The chloroform was separated and the aqueous layer was re-extracted with chloroform; this was repeated again after adjustment of the pH of the aqueous extract to pH 7 with dilute ammonia. The combined extracts yielded the solid *pyruvate* which crystallised twice from ethanol or ethyl acetate as pale yellow prisms (7·9 g., 85% yield from potassio-derivative), m. p. 157—158·5° (Found: C, 64·5; H, 6·3; N, 3·4. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·7%).

Ethyl β-[1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridyl*]-α-*hydroxyiminopropionate* (XVIII).—(i) The pyruvate (X) (3·73 g.) in alcohol (45 c.c.) was refluxed with hydroxylamine hydrochloride (0·77 g.) and anhydrous sodium acetate (0·88 g.) for 0·5 hr.; the solution was cooled and water (5 c.c.) added. The *oxime* (3·17 g., 82%), recrystallised from alcohol, had m. p. 186·5—189·5° (Found: C, 61·1; H, 6·3; N, 7·2. $C_{20}H_{24}O_6N_2$ requires C, 61·8; H, 6·2; N, 7·2%).

(ii) The crude potassio-derivative (3·8 g.) in alcohol (45 c.c.) was refluxed with hydroxylamine hydrochloride (0·77 g.) and sodium acetate (0·88 g.) for 0·5 hr., then concentrated to half its volume. The oxime (2·08 g., 58%) had m. p. and mixed m. p. 182—184°.

This ester (3·17 g.) was converted by 2N-sodium hydroxide (12·5 c.c.) on a boiling-water bath in 1·5 hr. into the *acid*, needles, m. p. 166—168° (2·50 g., crude) (Found: C, 59·9; H, 5·8; N, 7·8. $C_{18}H_{20}O_6N_2$ requires C, 60·0; H, 5·6; N, 7·8%).

1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetonitrile* (XX).—The hydroxyimino-acid (2·76 g.) was heated in acetic anhydride (5 c.c.) on a water-bath for 10 min., the anhydride removed under reduced pressure, and ethanol was added and then removed under reduced pressure. The crystalline *nitrile* was precipitated from a small volume of benzene by a few drops of light petroleum (b. p. 60—80°) as needles (1·82 g., 80%), m. p. 118—121° (Found: C, 68·4; H, 6·1; N, 10·0. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1; N, 9·4%).

1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetic Acid* (XI).—(i) The acetonitrile (0·23 g.) was refluxed overnight with ethanol (10 c.c.) and 2N-sodium hydroxide (5 c.c.). The alcohol was then removed and the aqueous alkaline solution extracted with benzene and then filtered. The filtrate was made acid by concentrated hydrochloric acid, and the precipitated red oil extracted with chloroform. After removal of the solvent the residue was dissolved in methanol from which prisms (0·23 g.), m. p. 158—161° (decomp.), were deposited. Crystallisation from methanol gave the *acetic acid*, m. p. 156·5—157° (decomp.) (Found: C, 64·3; H, 6·1; N, 4·7. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%).

(ii) The ester (X) (6·5 g.) was kept in 10% aqueous sodium hydroxide (31·2 c.c.) at 0° for 4·5 hr., then treated with 30% hydrogen peroxide (6·05 c.c.) and ice (*ca.* 17 g.) and kept for a further 16 hr. at 0°. Thereafter a further 2·6 c.c. of hydrogen peroxide were added and the solution was kept at 0° for a further 24 hr. Manganese dioxide (*ca.* 1 g.) was added, the solution filtered, and the filtrate made just acid to Congo-Red paper with concentrated hydrochloric acid. The oil was extracted with chloroform (3 × 25 c.c.), washed with water, and evaporated. The colourless solid residue was dissolved in methanol from which the acid (4·36 g., 78%), m. p. and mixed m. p. 157° (decomp.), separated.

(iii) The potassio-derivative (5·15 g.) was kept in 10% aqueous sodium hydroxide (22·5 c.c.) at 0° for 17 hr. Ice (12·5 g.) and 30% hydrogen peroxide (4·4 c.c.) were added and the solution

kept at 0° for 24 hr. A further 1·88 c.c. of hydrogen peroxide were added and the solution left for 3 days longer at 0°, then worked up as in (ii), to give the acid (2·91 g., 73·5%), m. p. 152—156° (decomp.). This reaction was repeated with the potassio-derivative (51·5 g.); after removal of the pyridylacetic acid (28 g.) the mother-liquor was concentrated to a syrup and treated with ethereal hydrogen chloride. The partially crystalline hydrochloride, after recrystallisation, gave 4-methyl-2-pyridone hydrochloride (3 g.), m. p. and mixed m. p. 166—167°.

Methyl 1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetate*.—(i) The nitrile (XX) (1·49 g.), suspended in dry methanol, was saturated at 0° with hydrogen chloride. After 20 hr. at 0° the methanol was removed under reduced pressure, and the residue dissolved in chloroform, washed with 2N-sodium carbonate, and evaporated. The residual ester was treated in a small volume of methanol with ethereal hydrogen chloride, which precipitated a slightly hygroscopic hydrochloride (1·37 g., 74%). Two recrystallisations from methanol–ether with a trace of dry hydrogen chloride gave the pure *hydrochloride*, m. p. 116·5—120° (Found: N, 4·3. $C_{18}H_{22}O_5NCl$ requires N, 3·8%). The hydrochloride in water dissociated to an oil; basification (2N-sodium carbonate) and extraction with chloroform gave the free *ester* which separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 64·5—67° (from ether at −10°) (Found: C, 64·9; H, 6·4; N, 4·7. $C_{18}H_{21}O_5N$ requires C, 65·3; H, 6·4; N, 4·2%).

(ii) The acid (XI) (0·63 g.) was treated in methanol (3 c.c.) with ethereal diazomethane [from methylnitrosourea (1·17 g.)]. Next morning unchanged acid (0·133 g.) was filtered off and the ester converted by ethereal hydrogen chloride into the hydrochloride, m. p. and mixed m. p. 117—120°. The base had m. p. and mixed m. p. 67—69°.

1-(3 : 4-*Dimethoxyphenethyl*)-2-*oxo*-4-*piperidylacetic Acid* (XII).—The acid (XI) (4·76 g.) was hydrogenated in methanol (140 c.c.) at room temperature and pressure in the presence of Adams catalyst (0·2 g.). (Uptake in 24 hr., 820 c.c. Theor., at 23°/757 mm., 797 c.c.) The catalyst was removed and the filtrate concentrated to *ca.* 20 c.c. to which ether (*ca.* 100 c.c.) was added. The *piperidylacetic acid* (4·13 g., 86%), m. p. 146—148°, separated from methanol–ether in prisms, m. p. 147·5—149·5° (Found: C, 63·4; H, 7·4; N, 4·6. $C_{17}H_{23}O_5N$ requires C, 63·5; H, 7·2; N, 4·4%).

1 : 2 : 3 : 4 : 6 : 7-*Hexahydro*-9 : 10-*dimethoxy*-2-*methoxycarbonylmethylbenzo*[a]*quinolizinium Iodide* (XXII).—The acid (XII) (0·23 g.) was dissolved in warm methanol (20 c.c.), and hydrogen chloride was passed into the solution to saturation at 0°. The solution was kept at room temperature overnight, then the solvent was removed. The residue was dissolved in chloroform and washed with 2N-sodium carbonate and water. Removal of the solvent gave the oily methyl ester (XXI). Without being crystallised (Pailer and Strohmayer [13b] record m. p. 57—58°) this was cyclised by phosphorus oxychloride (1 c.c.) and toluene (4 c.c.) at 95° for 5—10 min. The iodide was isolated as described by Pailer and Strohmayer and crystallised from water as yellow needles, m. p. 218—219·5° (lit., 218—220°) (Found: C, 48·5; H, 5·5; N, 2·9. Calc. for $C_{18}H_{24}O_4NI$: C, 48·5; H, 5·4; N, 3·1%), $\lambda_{max.}$ 232 (log ε 4·29), 300 (log ε 3·96), and 245 mμ (log ε 3·97) in water.

1-(3 : 4-*Dimethoxyphenylethyl*)-4-N-(3 : 4-*dimethoxyphenethyl*)*carbamoylmethyl*-2-*oxopiperidine* (XIII).—Ethyl chloroformate (1·19 g.) was added to a solution of the acid (XII) (3·21 g.) and triethylamine (1·01 g.) in dry dimethylformamide (12·5 c.c.) at −15° to −20° during 10—15 min. The mixture was kept at −10° for 10 min., then allowed to warm to 0° for 10 min., cooled to −5°, treated with 3 : 4-dimethoxyphenethylamine (2·71 g.) and triethylamine (1·01 g.) in dimethylformamide (5 c.c.), kept at room temperature overnight, and evaporated. The residue was dissolved in chloroform and washed with 2N-hydrochloric acid (20 c.c.), 2N-sodium carbonate (20 c.c.), and water. The chloroform was removed and the residue dissolved in ethyl acetate. The amide (4·05 g., 84%), m. p. 126—128°, separated in needles on cooling and an analytical sample, obtained from ethyl acetate, had m. p. 120—121° or 130—131°; these forms are interconvertible (Found: C, 67·3; H, 7·6; N, 5·9. Calc. for $C_{27}H_{36}O_6N_2$: C, 66·9; H, 7·5; N, 5·8%). Sugasawa and Oka [13c] give m. p. 130—131°.

2-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-2-iso*quinolylmethyl*)-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizinium Iodide Hydriodide* (XIV).—The amide (XIII) (9·70 g.) was heated in dry toluene (80 c.c.) with phosphorus oxychloride (20 c.c.) at 95° for 0·5 hr. Toluene and excess of phosphorus oxychloride were then removed and the residue was washed twice with dry light petroleum (b. p. 60—80°) by decantation. The residue was dissolved in water (100 c.c.) and a few c.c. were distilled under reduced pressure. On cooling, a small amount of crystalline material, m. p. 150°, was removed and, to the filtrate, sodium acetate (*ca.* 30 g.) and

then sodium iodide (24 g.) in water (40 c.c.) were added. The precipitated red oil was extracted with chloroform and washed with water. The recovered red gum was dissolved in methanol (*ca.* 60 c.c.) from which the *iodide hydriodide* (12·1 g., 85%), m. p. 193—195° (softens at 170°), separated; recrystallisation from methanol gave material of m. p. 193—195° (Found, in a sample dried at 60° *in vacuo*: C, 44·9; H, 5·0; N, 3·7; I, 36·0. $C_{27}H_{33}O_4N_2I,HI,H_2O$ requires C, 44·9; H, 5·0; N, 3·9; I, 35·1%). An air-dried sample had an indistinct m. p. (90—195°) owing to hydration (Found: C, 44·0; H, 5·1; N, 3·2. $C_{27}H_{33}O_4N_2I,HI,2H_2O$ requires C, 43·8; H, 4·9; N, 3·8%): at 100° *in vacuo* (2 hr.) it lost one molecule (Found: loss, 2·9. $C_{27}H_{33}O_4N_2I,HI,2H_2O$ requires H_2O, 2·4%). The absorption spectrum (solution in water) had maxima at 227·5 (log ε 4·61), 302·5 (log ε 4·29), and 455 mμ (log ε 4·29).

Use of sodium bromide instead of sodium iodide gave the *bromide hydrobromide*, pale yellow prisms, m. p. 193—195° (from methanol–ether) (Found: C, 50·2; H, 6·0; N, 4·1; Br, 24·1. $C_{27}H_{33}O_4N_2Br,HBr,2H_2O$ requires C, 50·3; H, 5·9; N, 4·3; Br, 24·8%), $\lambda_{max.}$ (in water) 242·5 (log ε 4·5), 305 (log ε 4·25), and 452 mμ (log ε 4·25). 1-(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)pentane dihydrobromide [30] had $\lambda_{max.}$ 242·5 (log ε 4·43), 305 (log ε 4·2), and 452 mμ (log ε 4·15).

(±)-*De-ethylemetine Dihydriodide* (XV).—*Racemate A*. The iodide hydriodide (XIV) (3·52 g.) was hydrogenated in methanol (150 c.c.) with Adams catalyst (0·2 g.) at room temperature and pressure. Absorption was slow but after 24 hr. the theoretical amount of hydrogen had been taken up and reduction ceased. The pale yellow solution was filtered and concentrated, prisms (1·5 g., 42%), m. p. 236—240° (softening at 234°), separating. Crystallisation from methanol gave the *dihydriodide A*, m. p. 247—249° (softening at 243°) (Found: C, 45·6, 45·2; H, 5·5, 5·6; N, 4·0, 3·3; I, 35·8. $C_{27}H_{36}O_4N_2,2HI$ requires C, 45·8; H, 5·4; N, 4·0; I, 35·8%). The base did not crystallise. Ethereal hydrobromic acid gave the *dihydrobromide*, m. p. 218—220° (from ethanol–ethyl acetate) (m. p. less sharp than for the dihydriodide, possibly owing to hydration) (Found: C, 48·4; H, 6·7; N, 3·8. $C_{27}H_{36}O_4N_2,2HBr,3H_2O$ requires C, 48·5; H, 6·6; N, 4·2%), $\lambda_{max.}$ (in water) 227 (log ε 4·17) and 282 mμ (log ε 3·85). The *dihydrogen dioxalate*, prepared from the dihydrobromide in the normal way, formed prisms (from methanol–ether) which softened at 120° and had m. p. 123—125° (meniscus at 140°) (Found: C, 56·0; H, 6·3; N, 4·3. $C_{27}H_{36}O_4N_2,2H_2C_2O_4,2H_2O$ requires C, 55·6; H, 6·6; N, 4·2%).

Racemate B. After separation of the dihydriodide A no further material could be obtained crystalline. However, evaporation gave a non-hygroscopic yellowish, amorphous powder, m. p. 210—220° (softening at 205°) (Found: C, 44·2; H, 5·7; N, 3·6%).

In a similar experiment, this product was dissolved in water, and the solution was made alkaline and extracted with chloroform. The base was treated with ethanolic oxalic acid. Ether was added. The precipitated oil crystallised slowly (1·06 g., 33%); on crystallisation from methanol–ethyl acetate, the *salt B* separated very slowly as prisms, m. p. 180° (decomp.) (Found: C, 59·4; H, 6·7; N, 4·5%). A mixed m. p. with the racemate A dihydrogen dioxalate was 112—140°.

In another experiment the amorphous dihydriodide (1·31 g.) was dissolved in methanol with warming; from the cooled solution ethereal hydrobromic acid precipitated a yellow gum. Crystallisation from methanol–ethyl acetate gave pale yellow prisms (0·31 g.), m. p. 225—230°. Recrystallisation gave prisms, soften at 218°, m. p. 224—228° (mixed m. p. with the dihydrobromide of racemate A, 212—227° (Found: C, 50·0; H, 6·7; N, 4·1; Br, 24·1. $C_{27}H_{36}O_4N_2,2HBr,2H_2O$ requires C, 49·8; H, 6·5; N, 4·3; Br, 24·6%), $\lambda_{max.}$ (in water) 228 (log ε 3·91) and 282 mμ (log ε 3·55).

De-ethylrubremetinium Bromide (XIII) (cf. ref. 23).—The amorphous racemates of de-ethylemetine dihydriodide, after removal of the crystalline racemate A—1·5 g. obtained from the mother-liquor by evaporation to dryness—were heated with potassium acetate (0·25 g.), mercuric acetate (5 g.) and acetic acid (1 c.c.) in water (32 c.c.) for 1 hr., then filtered. The mercurous acetate was washed with water, alcohol, and acetone. The washings were added to the first filtrate and the alcohol and acetone were removed under reduced pressure. A further quantity of mercuric acetate (2·5 g.) was added and the solution refluxed again for 2 hr. The solution was filtered and the mercurous acetate washed with water. The filtrate was heated to 90° and hydrogen sulphide was passed into the solution. Mercuric sulphide was filtered off and extracted exhaustively with boiling ethanol. The total filtrates were concentrated under reduced pressure to *ca.* 30 c.c. and treated with excess of 48% aqueous hydrobromic acid. The

[30] Osbond, *J.*, 1952, 4785.

orange-scarlet needles (0·80 g., 72%), m. p. 237—240° (soften at 230°), which separated, were collected. Recrystallisation from dilute hydrobromic acid gave *de-ethylrubremetinium bromide*, m. p. 233—235° (Found: C, 57·8; H, 5·9; N, 4·8. $C_{27}H_{29}O_4N_2Br,2H_2O$ requires C, 57·7; H, 5·9; N, 5·2%).

This oxidation product was also obtained by Pailer and Strohmayer [13b] but no experimental details or analyses are given; they record m. p. 215°.

Our product had $\lambda_{max.}$ (in H_2O) 257·5 (log ε 4·28), shoulder 283 (log ε 4·24), 300 (log ε 4·26), and 437·5 mμ (log ε 4·47). The absorption curve is identical with that given by Pailer and Strohmayer for this compound and with that for rubremetinium bromide.[24]

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RESEARCH DEPARTMENT, ROCHE PRODUCTS LIMITED,
WELWYN GARDEN CITY, HERTS.

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