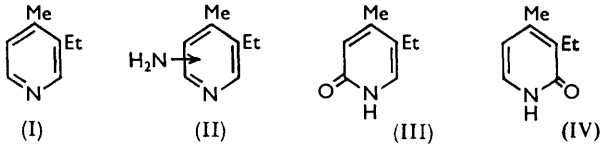
710. *Chemical Constitution and Amœbicidal Action. Part IV.* Synthesis of Emetine and Stereoisomers of Emetine.*

By M. Barash, J. M. Osbond, and J. C. Wickens.

Stereoisomers of emetine (XXII) have been synthesised by three routes: (1) Catalytic reduction of the four dehydroemetines (XXI) has given 4 stereoisomers of emetine (XXII) (Aa_1, Ab_2, Bc_1, and Bd_1). Paper chromatography showed only one of these isomers (Aa_1) to be inseparable from emetine. The physicochemical properties were in close agreement with those of emetine, and (±)-Aa_1 had slightly more than half the amœbicidal activity of (+)-emetine dihydrochloride. Resolution of the base of (±)-Aa_1 gave optically active salts indistinguishable from natural emetine salts. (2) Catalytic reduction of tetradehydroemetinium chloride hydrochloride (XXIII; A) led to the predominant formation of (±)-isoemetine (Ab_2) with a small amount of (±)-emetine (Aa_1). (3) Catalytic reduction of the esters (XXV; A and B) with subsequent transformations led to the formation of the above four emetine isomers.

The correct structure (XXII) for emetine, suggested by Robinson [1] on biogenetic grounds, was confirmed independently by Openshaw [2] and Pailer [3] and their co-workers, and (±)-rubremetinium bromide has been synthesised by three groups of workers.[4,5,6] In addition a total synthesis of emetine has been described by Preobrazhenskii and Evstigneeva and their co-workers,[7] and a partial synthesis by Battersby, Davidson, and Harper.[8] A summary [9] of our synthetic work was followed by a stereospecific synthesis of emetine by Battersby and Turner,[10] which caused us to re-examine some of our conclusions and to make a correction.[11]

As emetine (XXII) has four asymmetric centres (positions 2, 3, 11b, and 1'), 8 racemic and 16 optical isomers are possible. To apply the synthesis of de-ethylemetine, described in Part III,* to emetine, it was necessary to prepare the pyridone (III).

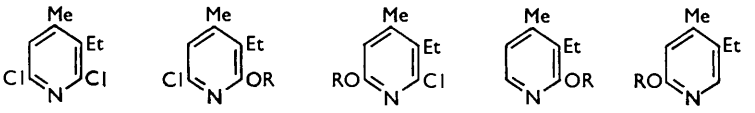


β-Collidine (I) with sodamide in dimethylaniline gave a mixture of the 2- and 6-aminopyridine (II) which was converted into the pyridones (III) and (IV) and separated by crystallisation, but the yield was low and the unwanted isomer (IV) predominated. An alternative route employed 2,6-dichloro-5-ethyl-4-methylpyridine [12] (V) which with one

* Part III, *J.*, 1959, 2157.

[1] Robinson, *Nature*, 1948, **162**, 524.
[2] Battersby and Openshaw, *J.*, 1949, 559, 567, 3207.
[3] Pailer, *Monatsh.*, 1948, **78**, 331; Spath and Pailer, *ibid.*, p. 348; Pailer, *ibid.*, 1948, **79**, 127; Pailer and Porschinski, *ibid.*, 1949, **80**, 94.
[4] Battersby, Openshaw, and Wood, *J.*, 1953, 2463.
[5] Ban, *Pharm. Bull.* (*Japan*), 1955, **3**, 47.
[6] Pailer and Beier, *Monatsh.*, 1957, **88**, 830.
[7] Preobrazhenskii, Evstigneeva, Levchenko, and Fedyushkina, *Doklady Akad. Nauk S.S.S.R.*, 1951, **81**, 421; Evstigneeva, Livshits, Bainova, Zakharkin, and Preobrazhenskii, *Zhur. obschei Khim.*, 1952, **22**, 1467; Evstigneeva, *ibid.*, 1958, **28**, 2458; Evstigneeva, Glushkov, and Preobrazhenskii, *ibid.*, p. 2463.
[8] Battersby, Davidson, and Harper, *Chem. and Ind.*, 1957, 983.
[9] Barash and Osbond, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957; Barash and Osbond, *Chem. and Ind.*, 1958, 490.
[10] Battersby and Turner, *Chem. and Ind.*, 1958, 1324; cf. Burgstahler and Bithos, *J. Amer. Chem. Soc.*, 1959, **81**, 503.
[11] Osbond, *Chem. and Ind.*, 1959, 257.
[12] Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 338.

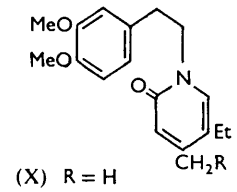
equivalent of sodium isopropoxide, sodium benzyloxide, or potassium diphenylmethoxide gave a mixture of the isomers (VI) and (VII) (R = Pr^i, CH_2Ph, or $CHPh_2$). It was hoped



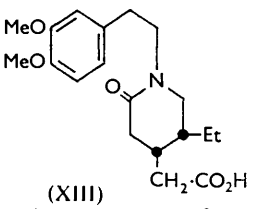
(V) (VI) (VII) (VIII) (IX)

that the condensation with a bulky group (*e.g.*, diphenylmethyl) would occur chiefly at the less hindered 2-position. The mixture (VI + VII; R = Pr^i) was dechlorinated by hydrogenolysis to give the ethers (VIII + IX; R = Pr^i) which on acid hydrolysis gave the pyridones (III; 47%) and (IV; 9%). Alternatively, the mixture (VI + VII; R = Pr^i) was hydrolysed and then dechlorinated. The mixture of benzyl ethers (VI + VII) was hydrogenated to give predominantly the pyridone (III). The condensation with potassium diphenylmethoxide was the most favourable as it gave chiefly the ether (VII; R = $CHPh_2$). Hydrogenolysis gave the pure pyridone (III) in one step.

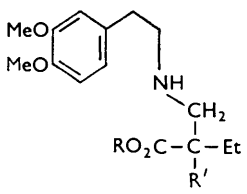
The structures of the pyridones (III) and (IV) were assigned on the following considerations. By analogy [13] it was expected that, in the amidation of β-collidine (I), isomer (IV) would predominate, whereas in the condensation of the dichloro-compound (V) with potassium diphenylmethoxide the isomer (III) was expected. The pyridone (III) had $\lambda_{max.}$ 298 mμ, and the isomer (IV) 293 mμ; 5- and 3-methyl-2-pyridones [13] showed a parallel difference, namely 303 and 295 mμ respectively (cf. also ref. 14). Compound (III) was converted into the two acetic acid derivatives (XIII; A and B) (see below) which were identical with those obtained by a different route [5] and were converted eventually into (±)-rubremetinium bromide (XXIV).



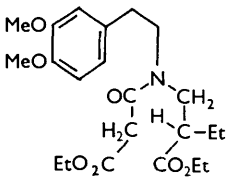
(X) R = H
(XI) R = CO·CO_2Et
(XII) R = CO_2H



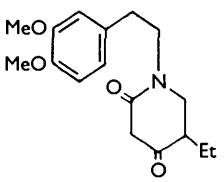
(XIII)
A, m.p. 154–156°
B, m.p. 152–153°



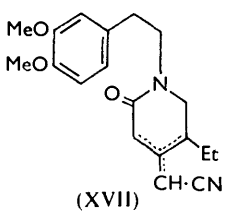
(XIV)



(XV)



(XVI)

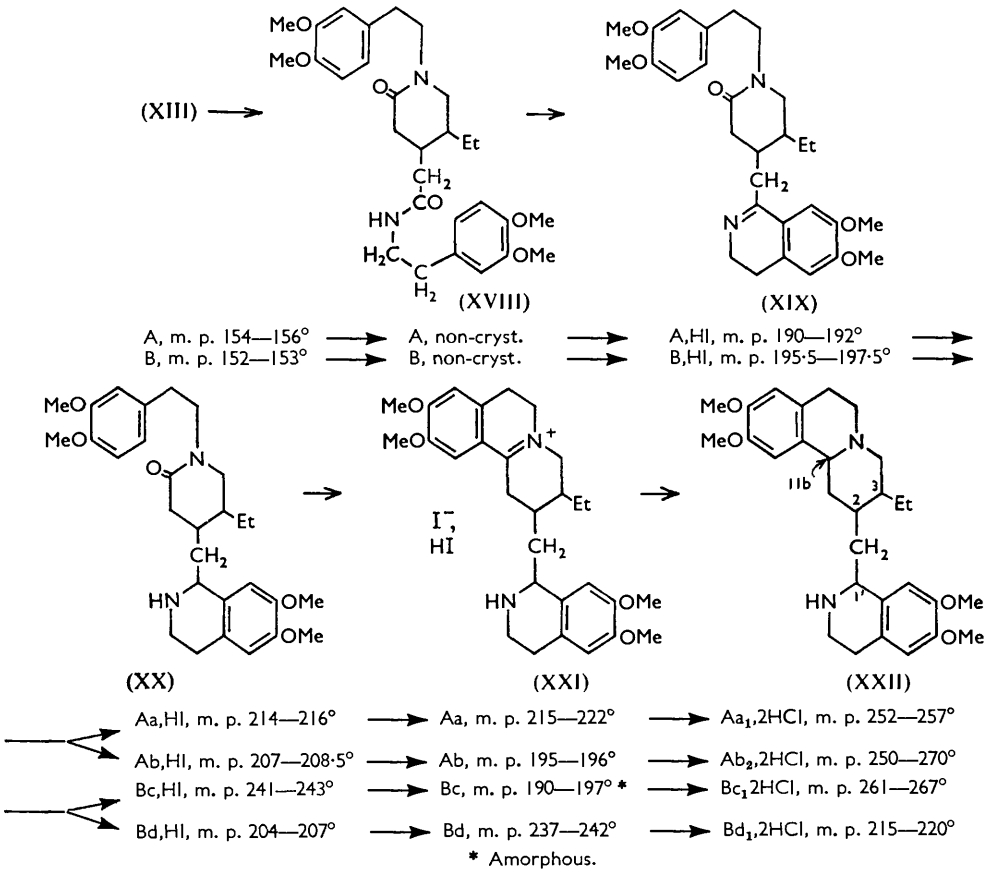


(XVII)

Condensing the pyridone (III) with 3,4-dimethoxyphenethyl iodide in t-butyl alcohol with potassium hydroxide gave the *N*-substituted pyridone (X). This with ethyl oxalate gave the potassio-salt of the pyruvic ester which with dilute acid gave the ester [15] (XI). It was assumed that only the active 4-methyl group would participitate in this reaction. Oxidation of the ester (XI) or the potassio-salt with alkaline hydrogen peroxide gave the corresponding acetic acid (XII) which, on melting, is decarboxylated to the pyridone (X).

[13] Seide, *Ber.*, 1924, **57**, 1805.
[14] Bradlow and Vanderwerf, *J. Org. Chem.*, 1951, **16**, 73.
[15] Cf. Adams and Schrecker, *J. Amer. Chem. Soc.*, 1949, **71**, 1186; and Part III.

Hydrogenation of the acetic acid (XII) with Adams catalyst gave the two stereoisomeric 2-piperidone acids (XIII), A, m. p. 154—156° (70%), and B, m. p. 152—153° (15%); a mixed m. p. between the two gave a strong depression. It was later shown [16] that the A series has the *trans*- and the B series the *cis*-configuration. Ban [5] later described a synthesis of the acids (XIII) (non-crystalline) which appeared more convenient than the above route. The Mannich base (XIV; R = H, R′ = CO_2H) was decarboxylated to give the monocarboxylic acid (XIV; R = R′ = H), now obtained crystalline, and esterified (R = Et). Treatment with ethoxycarbonylacetyl chloride yielded the diester (XV) which was converted into the ketone (XVI) and then crystallised as a monoethanol solvate. However, several attempts to repeat the condensation of the ketone (XVI) with ethyl cyanoacetate and subsequent transformations under Ban's conditions [5] gave only a trace of crystalline acid (XIII; A). However, condensing the ketone (XVI) with cyanoacetic acid gave a good yield of mixed unsaturated nitriles (XVII), which on esterification, reduction, and hydrolysis gave the two crystalline acids (XIII) A (56%) and B (12%) in good overall yield.



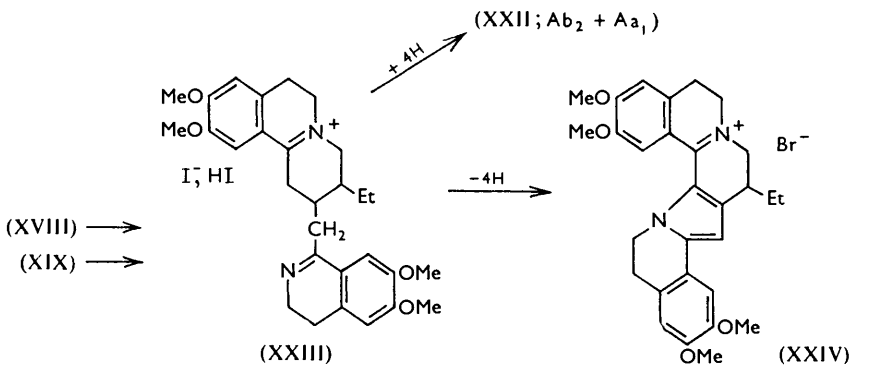
Treatment of the separated acids (XIII) A and B with triethylamine and ethyl chloroformate gave the corresponding ethoxyformic anhydrides, which with 3,4-dimethoxyphenethylamine afforded the amides (XVIII, A and B). It has already been shown [17] that cyclisation of *NN*′-bis-(3,4-dimethoxyphenethyl)glutardiamide with phosphoric oxide

[16] Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *Chem. and Ind.*, 1958, 491; Part V, following paper.
[17] Osbond, *J.*, 1951, 3464.

in toluene resulted in γ-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)-*N*-(2-3,4-dimethoxyphenethyl)butyramide as well as 1,3-bis-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)propane. Application of this method to the two amides (XVIII) resulted in good yields of the monocyclised dihydroisoquinolines (XIX), isolated as their hydriodides: it will be shown later that the possible alternative cyclisation involving the piperidone did not occur. The structure of compound (XIX) was confirmed by cyclising isomer A further with phosphorus oxychloride to the benzo[*a*]quinolizinium salt (XXIII A) (see below). Hydrogenation of compound (XIX) was effected with Adams catalyst in methanol or dilute acid, or with Raney nickel or sodium borohydride. Isomer (XIX A) gave a mixture of products (XX; Aa, 55% and Ab, 45%); similarly, the isomer (XIX B) gave more (XX; Bc, 55%) than (XX; Bd, 26%).

The hydriodides of bases (XX) were cyclised by phosphorus oxychloride in chloroform and toluene in uniformly high yield.

The final step involves reduction of the dehydroemetinium salts (XXI) at the 11b centre either catalytically (Adams) or with potassium borohydride. Each dehydroemetinium salt (XXI) yielded essentially only one stereoisomer of emetine, isolated as their dihydrochlorides which were the most suitable for biological testing. *E.g.*, the salt (XXI; Aa) gave the emetine isomer (XXII; Aa_1) in 80% yield. Two isomers are theoretically possible in these reductions and in some cases a very small amount of a second compound was detected. *E.g.*, in addition to (XXII; Aa_1), 5—10% of a non-crystalline material considered to be (XXII; Aa_2) was found by paper chromatography and isolated; however, its structure was not established with certainty. In order to ensure homogeneity of the isomers (XXII) and to detect (±)-emetine, paper chromatography was employed extensively. By this means all four isomers Aa_1, Ab_2, Bc_1, and Bd_1 were separated and only one (XXII; Aa_1) could not be separated from emetine (see Table 1). This most abundant isomer (XXII; Aa_1) was considered to be (±)-emetine on the following evidence. The melting points of the base, dihydrochloride, and dihydriodide were in close agreement with those of authentic optically active specimens, and infrared comparison showed no differences except in the case of the dihydrochloride. The dihydrochloride of (±)-Aa_1, when tested against *E. histolytica* in weanling rats by a modification of the Jones [18] method, had slightly more than half the activity of (±)-emetine dihydrochloride, and the same activity *in vitro* (see Table 1, revised values [11]). It should be noted that the other stereoisomers of emetine (XXII; Ab_2, Bc_1, and Bd_1) do



not approach this high level of amœbicidal activity *in vivo* and cannot be considered to be (±)-emetine, in conformity with their chromatographic behaviour. Resolution of isomer

[18] Jones, *Ann. Trop. Med. Parasitol.*, 1956, **40**, 130.

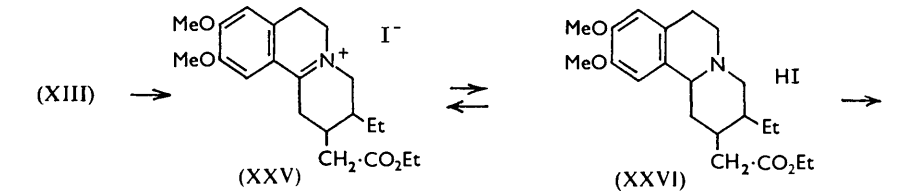
(XXII; Aa_1) with two mols. of (+)-dibenzoyltartaric acid gave the bis-(−)-dibenzoyltartrate of (Aa_1), which was identical with an authentic specimen prepared by Dr. Brossi [19] as shown by m. p., mixed m. p., paper chromatography, infrared spectra, and rotation. From the synthetic bis-(−)-dibenzoyltartrate, the (+)-dihydrochloride and (+)-dihydriodide were prepared, and again comparison with authentic specimens showed no differences (see p. 3541). It follows if compound (XXII; Aa_1) is (±)-emetine, then isomer (XXII; Ab_2) is isoemetine as this isomer is epimeric with emetine at position 1′.

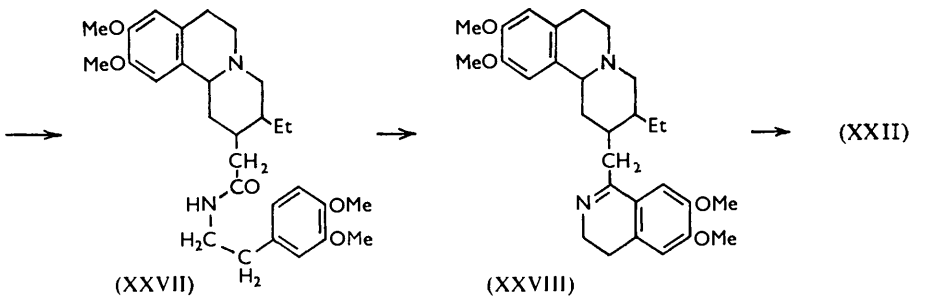
TABLE 1.

Stereoisomer of emetine,2HCl	Amœbicidal *in vivo* test: CD_{50} (mg./kg.)	Amœbicidal *in vitro* test: m.c. (g./ml.)	R_F (emetine = 1) *
Aa_1	6·25	10	1·00
Ab_2	64·6	10,000	0·62 †
Bc_1	133	1000	0·79 †
Bd_1	200	1000	0·67 †
(+)-Emetine,2HCl	6·25—12·5, 4—8	10—100	1·00

* These values are: Distance travelled by substance/Distance travelled by emetine, in ethyl methyl ketone–2N-aqueous hydrochloric acid on Whatman No. 1 paper.
† Separation from emetine can be effected.

The above work located (±)-emetine as being in the A series; in addition, the paper-chromatographic, physical, and biological properties of compound (XXII; Aa_1) in relation to the other isomers allowed a second approach to be made, namely, the simultaneous





* The transformation of (XXVI; B) ⟶ (XXVII; B) ⟶ (XXVIII; B) ⟶ emetine isomers (XXII; Bc_1) and (Bd_1) was carried out by Brossi and Schnider.[19] Their compounds have been included in the above chart for completeness. The conditions used by Brossi and Schnider for the above reactions were used by us in the corresponding A series.

reduction of the two double bonds in tetradehydroemetine (cf. XXIII; A). Cyclisation of the amide (XVIII; A) to give a pentacyclic base (XXIII; A) was best effected with phosphorus oxychloride alone; alternatively, cyclisation of the base (XIX; A) gave the

same iodide hydriodide A of (XXIII). Similarly, the isomeric amide (XVIII; B) gave the quaternary salt B of (XXIII). Dehydrogenation of a salt of (XXIII; A) with mercuric acetate, etc., gave (±)-rubremetinium bromide (XXIV) in good yield, and comparison with an authentic specimen showed them to be identical. Catalytic reduction (Adams) of the chloride hydrochloride derived from (XXIII; A) gave (±)-isoemetine (XXII; Ab_2) (in 60% yield), identified by the R_F value, infrared spectrum, and amœbicidal activity *in vivo*. The mother-liquor gave mixtures of (±)-isoemetine (Ab_2) and (±)-emetine (Aa_1), as shown by paper chromatography, but the small quantities present did not allow us to obtain pure (±)-emetine by this route. Openshaw and Wood [20] showed that catalytic reduction of a tetradehydroemetine salt, probably as (XXIII),[20,21] gave only isoemetine. Reduction with other catalysts under various conditions and with potassium borohydride in methanol gave substantially the same result. Catalytic reduction of an isomeric chloride hydrochloride (cf. XXIII; B) gave rise almost certainly to the emetine isomer (XXII; Bc) as shown by the melting point and paper chromatography, but this was not firmly established. Evstigneeva and her co-workers [8] obtained a salt (XXIII) (m. p. 257—258°; A or B?) by a different route which on hydrogenation (Adams) gave an isomer considered to be (±)-emetine, together with a second isomer.

A third approach to the synthesis of stereoisomers of emetine was carried out as shown in the flow sheet above. Esterification of the acids (XIII; A and B) gave the corresponding esters, which without isolation were cyclised to give the quaternary iodides (XXV; A and B). These on catalytic reduction (Adams) gave in each case only one isomer, isolated as their hydriodides (XXVI) in 91 and 95% yield respectively. In the case of salt (XXV; A) many experiments were carried out with different catalysts under varying conditions and by chemical reduction, such as potassium borohydride, alkaline sodium dithionite,[22] formic acid on the anhydro-base,[23] in an attempt to obtain the other isomer, but in all cases only the isomer (XXVI; A) was obtained; zinc and hydrochloric acid [24] gave no crystalline material. Treatment of salts (XXVI; A and B) with mercuric acetate gave the dehydro-esters (XXV; A and B) in high yield.

Condensing of the amino-acid corresponding to (XXVI; A) with 3,4-dimethoxyphenethylamine gave the amide (XXVII; A). Brossi and Schnider [19] later obtained the amide (XXVII; A) from 3-ethyl-1,2,3,4,5,6-hexahydro-9,10-dimethoxy-2-oxo-11b*H*-benzo[*a*]quinolizine,[4,25] identity being provided by m. p., mixed m. p., and infrared-spectral comparison. The hydriodide, m. p. 227—228°, of base (XXVII; A) was not identical with either hydriodide of base (XX; Aa or Ab), and this confirms the view that in our first synthesis the direction of monocyclisation was (XVIII) ⟶ (XIX). Cyclisation of the base (XXVII; A) with phosphorus oxychloride gave (±)-*O*-methylpsychotrine dihydrobromide (XXVIII; A) which on hydrogenation (Adams) led to approximately equal amounts of compounds (XXII; Ab_2) [(±)-isoemetine] and (XXII; Aa_1) [(±)-emetine] (45, 40%), whose identities were established by m. p.s, mixed m. p.s, paper chromatography, and infrared-spectral comparison. Preobrazhenskii and his co-workers [7] and Battersby and Turner [10] described the isolation of emetine by this route. Both groups were using the *trans*-isomer (XXVII) which corresponds to our A series [16] (cf. van Tamelen and his co-workers [26]).

During this work Brossi and Schnider [19] prepared an acid corresponding to (XXVI) by

[19] Brossi, Schnider *et al.*, unpublished work.
[20] Openshaw and Wood, *J.*, 1952, 391.
[21] Battersby and Openshaw, *J.*, 1949, S67; Hazlett and McEwen, *J. Amer. Chem. Soc.*, 1951, **73**, 2578; Tietz and McEwen, *ibid.*, 1953, **75**, 4945.
[22] Sugasawa, Akahoshi, and Suzuki, *J. Pharm. Soc. Japan*, 1952, **72**, 1273.
[23] De Benneville and Macartney, *J. Amer. Chem. Soc.*, 1950, **72**, 3073; Leonard, Thomas, and Gash, *ibid.*, 1955, **77**, 1556.
[24] Weisenborn and Diassi, *ibid.*, 1956, **78**, 2022; Klohs, Keller, Williams, and Kusserow, *ibid.*, 1957, **79**, 3763.
[25] Brossi, Lindlar, Walter, and Schnider, *Helv. Chim. Acta*, 1957, **41**, 119.
[26] van Tamelen, Aldrich, and Hester, *J. Amer. Chim. Soc.*, 1957, **79**, 4817.

a different route. Esterification and examination of the hydriodide by m. p., mixed m. p., and infrared spectroscopy showed it to be identical with our salt (XXVI; B). They had already transformed this by way of (XXVII; B) and (XXVIII; B) into two emetine isomers (XXII) which were shown to be identical with our emetine stereoisomers (XXII; Bc_1 and Bd_1) by paper chromatography, infrared-spectral comparison, m. p.s, mixed m. p.s, and amœbicidal activity *in vivo*.

Experimental

5-Ethyl-4-methyl-2-pyridone (III) *and 3-Ethyl-4-methyl-2-pyridone* (IV).—(*a*) Sodamide (from sodium, 5·75 g.), dimethylaniline (22·5 c.c.), and β-collidine (24·2 g.) were heated at 170° for 5 hr., then cooled. Methanol, water, and sodium hydroxide solution were added and the mixture was extracted 6 times with chloroform. The basic material was distilled (b. p. 80—100°/0·7 mm.) to give an oil (11·35 g., 42%), n_D 1·5562, which was a mixture of 5-ethyl-4-methyl-2- and -6-aminopyridine. The mixture (10·8 g., 0·079 mole) was dissolved in 2N-sulphuric acid. Sodium nitrite (0·079 mole) in water (10 c.c.) was slowly added at 5°, and the whole warmed to 90° for 0·5 hr., made alkaline, and taken to dryness under reduced pressure. Extraction with ethanol yielded on distillation a mixture of pyridones (8·2 g., 75%), b. p. 150—158°/0·9 mm. The *3-ethyl-4-methyl-2-pyridone*, which was predominant, crystallised from ethyl acetate as plates, m. p. 169·5—172° (Found: C, 70·25; H, 8·2; N, 10·3. $C_8H_{11}ON$ requires C, 70·1; H, 8·1; N, 10·2%), $\lambda_{max.}$ (in H_2O) 230 (log ε 3·67), 293 mμ (log ε 3·83). After crystallisation from ethyl acetate the required *5-ethyl-4-methyl-2-pyridone*, m. p. 160·5—161·5°, was obtained in low yield as prisms (Found: C, 70·4; H, 7·9; N, 10·65%), $\lambda_{max.}$ (in H_2O) 230 (log ε 3·81), 298 (log ε 3·77).

(*b*) (i) To a solution of sodium (2·54 g.) in dry benzyl alcohol (90 c.c.) was added 2,6-dichloro-5-ethyl-4-methylpyridine [12] (18·9 g.). The solution was heated on a boiling-water bath for 9 hr., then under reflux for 0·75 hr. The benzyl alcohol was removed, water was added, the whole was extracted with ether, and the extract was washed with water and dried (K_2CO_3). Two distillations gave essentially *6-benzyloxy-2-chloro-3-ethyl-4-methylpyridine* (VII; R = CH_2Ph) (23·07 g., 88%), b. p. 150°/0·6 mm., n_D^{20} 1·5680 contaminated with a certain amount of the other isomer (Found: C, 69·3; H, 6·1; N, 5·4; Cl, 13·1. $C_{15}H_{16}ONCl$ requires C, 68·85; H, 6·2; N, 5·35; Cl, 13·45%).

This base (2·5 g.) was hydrogenated (palladium–charcoal) in methanol at room temperature and atmospheric pressure, yielding essentially the hydrochloride (0·9 g.), m. p. 161—168°, of 5-ethyl-4-methyl-2-pyridone. This salt yielded a base whence crystallisation from ethyl acetate afforded pure 5-ethyl-4-methyl-2-pyridone as prisms, m. p. 160—162°, identical with that prepared by method (a), together with a small amount of the 3-ethyl-4-methyl-2-pyridone.

(ii) Potassium (8·6 g.) was refluxed with diphenylmethanol (55·2 g.) in xylene (400 c.c.) in a nitrogen atmosphere for 20 hr. 2,6-Dichloro-3-ethyl-4-methylpyridine (38 g.) was then added and refluxing continued for a further 24 hr. The xylene was washed with water and evaporated to dryness under reduced pressure. The residue was crystallised twice from methanol, to give *2-chloro-6-diphenylmethoxy-3-ethyl-4-methylpyridine* (VII; R = $CHPh_2$) (26·1 g.), m. p. 104—105° (Found: C, 75·2; H, 5·95; N, 4·2; Cl, 10·3. $C_{21}H_{20}ONCl$ requires C, 74·7; H, 6·0; N, 4·15; Cl, 10·5%). The other isomer, *6-chloro-2-diphenylmethoxy-3-ethyl-4-methylpyridine* was isolated in small amount from the mother-liquor and after crystallisation from methanol had m. p. 94—95° (Found: C, 74·0; H, 5·8; N, 4·0%). The 2-chloro-ether (26·1 g.) in ethanol (600 c.c.) and water (10 c.c.) containing sodium acetate (14 g.) was hydrogenated (3 g. of palladium–charcoal) at room temperature and atmospheric pressure. This yielded the 5-ethyl-4-methyl-2-pyridone (8·57 g.), m. p. 160—161°. In a similar way the other isomer yielded on hydrogenolysis the 3-ethyl-4-methyl-2-pyridone.

(*c*) 2,6-Dichloro-3-ethyl-4-methylpyridine (19 g.) in dry xylene (100 c.c.) was added to sodium isopropoxide [from sodium (2·3 g.) in propan-2-ol (75 c.c.)] suspended in xylene (100 c.c.) and refluxed for 16 hr. The solution was filtered and the product distilled, to give essentially *2-chloro-3-ethyl-6-isopropoxy-4-methylpyridine* (VII; R = Pr^i) (17·77 g.), b. p. 78—80°/0·8 mm., n_D 1·5075, contaminated with the other isomer (Found: C, 61·5; H, 7·7; N, 6·45; Cl, 16·6. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·55; N, 6·6; Cl, 16·6%).

(*c'*) The above chloro-isopropoxypyridine (15·4 g.) in methanol (150 c.c.) was hydrogenated in the presence of palladised charcoal (4 g.) and sodium acetate (12 g.) at room temperature and atmospheric pressure. The *5-ethyl-2-isopropoxy-4-methylpyridine* (IX; R = Pr^{i}) (14·73 g.), b. p. 132—134°/7·2 mm., was distilled (Found: C, 73·8; H, 9·8; N, 7·55. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6; N, 7·8%). This product (2·4 g.) was heated with concentrated hydrochloric acid (15 c.c.) in a sealed tube at 118° for 4·5 hr. The resulting 5-ethyl-4-methylpyridone was extracted with chloroform and crystallised from ethyl acetate as prisms (47%), m. p. 159·5—162°. From the mother-liquor 9% of the isomeric pyridone was obtained.

(*c''*) Crude 2-chloro-3-ethyl-6-isopropoxy-4-methylpyridine (42 g.) was refluxed in 48% hydrobromic acid (400 c.c.) for 0·5 hr. Hydrobromic acid was removed, and the solution was made slightly alkaline with aqueous sodium carbonate. The solid that separated crystallised from ethyl acetate and then alcohol, to give *6-chloro-5-ethyl-4-methyl-2-pyridone* (9·47 g.), m. p. 174—176° (Found: C, 55·9; H, 5·4; N, 7·8; Cl, 20·8. $C_8H_{10}ONCl$ requires C, 56·0; H, 5·9; N, 8·2; Cl, 20·7%).

The above 6-chloro-2-pyridone (1·55 g.) in methanol (25 c.c.) was hydrogenated at room temperature and atmospheric pressure in the presence of sodium acetate (1·5 g.) and palladised charcoal (1 g.), yielding 5-ethyl-4-methyl-2-pyridone (0·75 g.), m. p. 159—161°, identical with that obtained above.

3-Methyl-2-pyridone.—Sodium nitrite (3·7 g.) in water (10 c.c.) was added to 2-amino-3-methylpyridine (5·0 g.) in sulphuric acid (concentrated acid 5·5 c.c., in water, 42 c.c.) at 5°. After 1 hr. at 10° the solution was heated at 90° for 1 hr. Potassium carbonate was added, and the solution concentrated to dryness. The residue was extracted with boiling ethanol. The ethanol extracts were combined, evaporated, and sublimed at 100°/0·5 mm. to give the pyridone (2·7 g.), which on crystallisation from benzene had m. p. 141—143° (Seide [13] gives m. p. 140°), $\lambda_{max.}$ (in H_2O) 226 (log ε 3·84), 295 mμ (log ε 3·93).

5-Methyl-2-pyridone.—This *isomer* (2·9 g.) was prepared similarly from 2-amino-5-methylpyridine (5 g.) and after sublimation at 110°/1·0 mm. and crystallisation from benzene had m. p. 184—188° (Found: C, 66·0; H, 6·5; N, 12·8. C_6H_7ON requires C, 66·1; H, 6·5; N, 12·8%), $\lambda_{max.}$ (in H_2O) 227 (log ε 3·91); 303 mμ (log ε 3·79).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-4-methyl-2-pyridone (X).—5-Ethyl-4-methyl-2-pyridone (2·72 g.) was added to a solution of potassium hydroxide (1·32 g.) in water (1 c.c.) and t-butyl alcohol (80 c.c.), followed by 3,4-dimethoxyphenethyl iodide (5·84 g.), and the solution was refluxed for 4 hr. The butanol was removed, water added, the whole extracted 3 times with benzene, the extracts were washed with water, and the product converted into the *hydrochloride* (4·28 g.), m. p. 199—201·5° (decomp.) (Found: C, 64·2; H, 7·3; N, 4·0; Cl, 10·5. $C_{18}H_{23}O_3N$,HCl requires C, 64·5; H, 7·2; N, 4·15; Cl, 10·5%).

The *pyridone*, obtained from the hydrochloride separated from ethyl acetate–ether as prisms, m. p. 72—75·5° (Found: N, 4·7. $C_{18}H_{23}O_3N$ requires N, 4·65%).

Ethyl 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-pyridylpyruvate (XI).—Absolute ethanol (2·85 c.c.) was added dropwise to potassium (0·43 g.) under dry ether (10 c.c.), followed by ethyl oxalate (1·6 g.) in ether (6 c.c.) at 0°. The pyridone (X) (3·01 g.) in dry benzene (40 c.c.) and ether (140 c.c.) was added and the solution refluxed for 24 hr. After cooling to 0° for 4 hr. the yellow potassio-salt (3·01 g., 85% based on pyridone used) was filtered off and washed with ether. Treatment of this salt with 2N-sulphuric acid, extraction with chloroform, and crystallisation from ethyl acetate gave the *ester*, m. p. 141·5—142·5° (Found: C, 65·7; H, 7·0; N, 3·4. $C_{22}H_{27}O_6N$ requires C, 65·8; H, 6·8; N, 3·5%).

The potassio-salt of the pyruvate (3 g.) in 10% aqueous sodium hydroxide (12·4 c.c.) was kept at 0° for 18 hr. A small amount of ice was added, followed by 30% hydrogen peroxide (2·41 c.c.); after 24 hr. at 0° a further quantity of hydrogen peroxide (1·03 c.c.) was added. After a further 24 hr. at 0° manganese dioxide (0·1 g.) was added, the mixture was filtered, and the filtrate made slightly acid with hydrochloric acid and extracted with chloroform. Treatment of the product with ethereal hydrogen chloride gave the *acetic acid hydrochloride* (cf. XII) which crystallised from methanol–ether as prisms (1·92 g., 76·5%), m. p. 160·5—162·5° (decomp.) (Found: C, 59·3; H, 6·7; H, 3·3. $C_{19}H_{23}O_5N$,HCl requires C, 59·8; H, 6·3; N, 3·7%). The free *acid* (obtained from the hydrochloride) and crystallised from methanol had m. p. 154° (decomp.) (Found: N, 4·2. $C_{19}H_{23}O_5N$ requires N, 4·1%), $\lambda_{max.}$ (in 2N-HCl) 228, 285, and 303 mμ (log ε 3·99, 3·68, and 3·71 respectively).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2,4-dioxopiperidine (XVI).—The 2,4-dioxopiperidine was

prepared by Ban's method [5] with some improvement of yield and crystallisation of intermediates. 3,4-Dimethoxyphenethylamine was condensed with formaldehyde and ethylmalonic acid to give the Mannich base, m. p. 157—158°. Decarboxylation was then effected in 60% acetic acid to give α-(3,4-dimethoxyphenethylaminomethyl)butyric acid, m. p. 155—156° (Found: C, 64·1; H, 8·2; N, 4·9. Calc. for $C_{15}H_{23}O_4N$: C, 64·2; H, 8·2; N, 4·9%), the overall yield for the two steps being 75%. Esterification of the acid with ethanol and hydrogen chloride, followed by treatment with the acid chloride of ethyl hydrogen malonate gave ethyl α-[*N*-(ethoxycarbonylacetyl)-*N*-(3,4-dimethoxyphenethyl)aminomethyl]butyrate. Dieckmann cyclisation, by sodium in xylene, of the diester, hydrolysis by 10% acetic acid, and decarboxylation gave the ketone as a crystalline *ethanol solvate*, m. p. 38—40°, in 62% overall yield (Found: C, 65·3; H, 8·1; N, 4·2. $C_{17}H_{23}O_4N,C_2H_5{\cdot}OH$ requires C, 64·95; H, 8·3; N, 4·0%).

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-1,2-*dihydro*-2-*oxo*-4-*piperidylacetic Acids* (XIIIA *and* B).—(i) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-pyridylacetic acid (6·91 g.) was hydrogenated in methanol (400 c.c.) in the presence of Adams catalyst (0·3 g.) at room temperature and atmospheric pressure. After 2—3 days the slow uptake of hydrogen ceased (*ca.* 2 mol.). The *acetic acid* (A) separated from methanol as prisms (4·56 g., 70%), m. p. 154—156° (Found: C, 65·2; H, 8·35; N, 4·5. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

From the mother-liquor, on concentration, the *acid* (B) separated as prisms (0·94 g., 14%), m. p. 152—153°. A mixed m. p. between A and B gave a marked depression (m. p. 130—135°) (Found: C, 65·3; H, 7·9; N, 3·9. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

(ii) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-2,4-dioxopiperidine ethanol solvate (70·3 g., 0·2 mole), dry cyanoacetic acid (39 g., 0·459 mole), dry ammonium acetate (5 g.), and glacial acetic acid (5 ml.) were dissolved in benzene (500 ml.) and refluxed in a Dean and Stark apparatus at 110° for 3 hr. Cyanoacetic acid (12 g., 0·141 mole), ammonium acetate (3 g.), and glacial acetic acid (5 ml.) were added and the whole was refluxed for a further 4 hr. Ammonium acetate (3 g.) was added and the mixture refluxed for a further 6 hr., then the bath-temperature was raised to 120°, the benzene distilling. The residual syrup was heated in the bath for a further 12 hr. at 120°, dissolved in benzene (200 ml.), washed 3 times with 2N-sodium carbonate, then with water, dried (Na_2SO_4), and evaporated. The mixture of unsaturated nitriles (XVII) (80 g.) was dissolved in absolute alcohol (600 ml.), saturated with hydrogen chloride at 0°, and refluxed for 2½ hr. with continued passage of hydrogen chloride. The alcohol was removed and water (*ca.* 300 ml.) added. The solution was extracted 3 times with benzene, washed twice with 2N-sodium carbonate, and dried (Na_2SO_4). The benzene was removed, and the resulting ethyl esters (75 g.) were hydrogenated in methanol (650 ml.) at room temperature and atmospheric pressure in the presence of Adams catalyst (0·5 g.) (uptake 4·4 l.) (theor. 4·9 l.). The catalyst was removed, and the solution was concentrated to *ca.* 600 ml., treated with potassium hydroxide (20·7 g.) in water (20 c.c.), and refluxed for 3½ hr.; water was then added and the methanol removed under reduced pressure. The aqueous solution was acidified, extracted 3 times with chloroform, dried (Na_2SO_4), and co-distilled twice with methanol; the residue was dissolved in methanol (300 ml.) and the first main crop was the almost pure acetic acid A. Fractional crystallisation of the mother-liquor gave a total amount of the pure A isomer, m. p. 154—156° [identical with A prepared as in (i)] (39·49 g., 56·5%). The isomer (B), m. p. 152—153° (8·34 g., 12%), was identical with the B isomer prepared in experiment (i). When the original Ban process [5] was attempted the gummy mixture of acids at the end yielded only a trace of acetic acid A after being seeded with our crystalline material.

N-(3,4-*Dimethoxyphenethyl*)-α-[1-(3,4-*dimethoxyphenethyl*)-5-*ethyl*-2-*oxo*-4-*piperidyl*]*acetamide* (XVIII; A *and* B).—The acetic acid (XIII; A) (2·79 g.) was treated in dry dimethylformamide (25 c.c.) at 0° with triethylamine (0·85 g.), followed by ethyl chloroformate (1·12 g.) in dry dioxan (4 c.c.) at −30° during 10 min. The mixture was kept at −30° for a further 5 min. and at −10° for 10 min. Then 3,4-dimethoxyphenethylamine (1·6 g.) and triethylamine (0·85 g.) in dimethylformamide (20 c.c.) were added during 10 min. with stirring, and the mixture was kept at room temperature overnight. The solution was concentrated to a thick syrup, dissolved in chloroform, and washed with 2N-hydrochloric acid, 2N-sodium carbonate, and water and dried (Na_2SO_4). This yielded a pale yellow gum (quantitative yield) which did not crystallise. In a similar way the acetic acid (XIII; B) was also converted into the amide (XVIII; B). Compounds of similar structure have been prepared by a different route by Evstigneeva *et al.*,[7] also non-crystalline.

4-(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-1-(3,4-*dimethoxyphenethyl*)-5-*ethyl*-2-*piperidone Hydriodides* (cf. XIX; A *and* B).—The amide (XVIII; A) [prepared from the corresponding acetic acid (XIII; A) (5·28 g.)] was treated in dry refluxing toluene (140 c.c.) with phosphoric oxide (50 g.) for ¾ hr. Further oxide (50 g.) was added and refluxing continued for a further 1¼ hr. The toluene was decanted and the residual material added to ice. The solution was extracted with ether, and aqueous potassium iodide was added. The *hydriodide* was extracted three times with chloroform, dried, and evaporated. The residue crystallised from methanol–ethyl acetate as yellow prisms [8·05 g.; 85% for the two steps from (XIII; A)], m. p. 190—192° (Found: C, 56·15; H, 6·5; N, 4·5. $C_{29}H_{38}O_5N_2$,HI requires C, 56·0; H, 6·3; N, 4·5%). $\lambda_{max.}$ (in H_2O) 230, 287 sh, 303, and 354 mμ (log ε 4·44, 3·81, 3·96, and 3·95 respectively). The *base* crystallised from ethyl acetate as pale yellow prisms, m. p. 122·5—124° (Found: C, 70·2; H, 7·8; N, 5·35. $C_{29}H_{38}O_5N_2$ requires C, 70·4; H, 7·7; N, 5·7%).

A similar result was obtained by using polyphosphoric acid instead of phosphoric oxide, although the yield was lower.

Similarly the amide (XVIII; B) was cyclised to give the corresponding *hydriodide*, m. p. 195·5—197·5°, as yellow prisms (from methanol–ethyl acetate) [76% yield (from XIII; B)] [mixed m. p. with (XIX; A) 187—189°] (Found: C, 56·25; H, 6·2; H, 4·3%].

1-(3 : 4-*Dimethoxyphenethyl*)-5-*ethyl*-4-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-2-*piperidone Hydriodides* [XX; Aa, Ab, (Bc), *and* (Bd)].—The hydriodide (5·0 g.) of base (XIX; A) was hydrogenated in methanol (75 c.c.) with Adams catalyst (0·1 g.) at room temperature and atmospheric pressure until one mol. had been absorbed. The solution was filtered and concentrated; on cooling, the *hydriodide* (cf. XX; Aa) separated as colourless prisms (2·6 g., 51·8%), m. p. 214—216° (Found: C, 55·5; H, 6·6; N, 4·4. $C_{29}H_{40}O_5N_2$,HI requires C, 55·8; H, 6·6; N, 4·5%), $\lambda_{max.}$ (in H_2O) 226 and 280 mμ (log ε 4·43 and 3·74). On concentration the second *hydriodide* (cf. XX; Ab) was obtained which after two recrystallisations separated from methanol–ether as pale yellow plates (2·05 g., 41%), m. p. 207—208·5° [mixed m. p. between (Aa) and (Ab) 203—208°] (Found: C, 56·3; H, 6·6; N, 4·5; I, 20·9%).

The amide hydriodide (cf. XIX; B) (4·26 g.) was reduced with potassium borohydride (1·0 g.) in methanol (100 c.c.) at room temperature to give two stereoisomers (XX; Bc and Bd). The hydriodide (cf. XX; Bc) (2·02 g., 55%) separated from methanol, in which it was sparingly soluble, as yellow plates, m. p. 244—246°. Catalytic reduction with Adams catalyst in methanol raised the amount to 82% (Found: C, 55·6; H, 6·8; N, 4·8%). From the mother-liquor of the potassium borohydride reduction, the epimer (XX; Bd) was isolated as the *hydriodide* after several crystallisations from methanol–ether as pale yellow clumps (1·21 g., 26%), m. p. 203—205° (Found: C, 56·3; H, 7·0; N, 4·7%).

3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*isoquinolylmethyl*)*benzo*[a]*quinolizinium Iodide Hydriodides* (cf. XXI; Aa, Ab, Bc, and Bd).—The reduced hydriodide (cf. XX, Aa) (4·0 g.) was dissolved in dry chloroform (40 c.c.) of which 5 c.c. were removed by distillation. Dry toluene (30 c.c.) and phosphorus oxychloride (14 c.c.) were added and the solution was refluxed on a water-bath for 0·5 hr. The reagents were removed and the resulting red gum was dissolved in hot water (4 extractions) to which potassium iodide was added and the *iodide hydriodide* was extracted with chloroform and crystallised from methanol as yellow prisms (3·8 g., 81%), m. p. 215—222° (decomp.) (Found: C, 47·9; H, 5·4; N, 3·7. $C_{29}H_{39}O_4N_2I$,HI requires C, 47·4; H, 5·5; N, 3·8%).

The reduced hydriodide (cf. XX; Ab) (2·4 g.) was cyclised in a similar way. The resulting *iodide hydriodide* separated as yellow prisms, m. p. 195—196° (2·25 g., 79%) (Found: C, 47·2; H, 5·7; N, 3·6%). An air-dried sample had m. p. 186—193° with softening at 180° (Found: C, 45·9; H, 5·7; N, 3·8; I, 34·0; H_2O, 4·1. $C_{29}H_{39}O_4N_2I$,HI,1·5H_2O requires C, 45·7; H, 5·7; N, 3·6; I, 33·3; H_2O, 3·5%), $\lambda_{max.}$ (in H_2O) 227, 290, 302·5, and 350 mμ (log ε 4·7, 3·8, 3·88, and 3·9).

The *isomer* (XXI; Bc) was obtained in a similar manner in good yield but did not crystallise. The amorphous salt separated from ethanol as a yellow solid, m. p. 190—197° (Found: C, 46·3; H, 5·1; N, 3·9; I, 34·6. $C_{29}H_{39}O_4N_2I$,HI,0·5H_2O requires C, 46·9; H, 5·5; N, 3·8; I, 34·2%).

The *iodide hydriodide* (XXI; Bd) was obtained in 70% yield as pale yellow crystalline nodules (from ethanol), m. p. 237—242° (Found: C, 46·95; H, 5·5; N, 3·65; I, 34·1%).

2-(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide Hydriodide* (*Tetradehydroemetinium Iodide Hydriodide*) (XXIII; A).—(*a*) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-piperidylacetic acid (XIII;

A) (0·69 g.) was converted into the amide (XVIII; A), which was dissolved in phosphorus oxychloride (13 c.c.), and heated at 95° for 0·5 hr. The excess of reagent was removed and the gum, after being washed once with light petroleum, was dissolved in ethanol and water and treated with excess of potassium iodide. The *iodide hydriodide* was extracted with chloroform and crystallised from methanol as yellow prisms, m. p. 172—175° (1·10 g., 75%) (Found, in air-dried sample: C, 44·2; H, 5·95; N, 3·5; I, 33·0; loss on drying 6·0. $C_{29}H_{37}O_4N_2I,HI,2{\cdot}5H_2O$ requires C, 44·8; H, 5·6; N, 3·6; I, 32·65; $2{\cdot}5H_2O$, 5·8. Found, in dried sample: C, 48·1; H, 5·4; N, 3·7; I, 34·9. $C_{29}H_{37}O_4N_2I,HI$ requires C, 47·6; H, 5·2; N, 3·8; I, 34·65%), $\lambda_{max.}$ (in H_2O) 227, 240 sh, 305, 354 mμ (log ε 4·6, 4·52, 4·20, and 4·19).

(ii) 4-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolylmethyl)-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-piperidone hydriodide (cf. XIX; A) (2·0 g.) was cyclised in chloroform (10 c.c.), toluene (11 c.c.), and phosphorus oxychloride (7 c.c.) at 95° for 0·75 hr. The iodide hydriodide was obtained as described above as yellow prisms (2·07 g.; 87%), m. p. and mixed m. p. 175—177°.

The acetic acid (XIII; B) (0·69 g.) was converted into the amide (XVIII; B), as in the example above, and cyclised with phosphorus oxychloride (2 c.c.) and toluene (10 c.c.) for 15 min. The product (XXIII; B) crystallised from methanol as the sparingly soluble *iodide hydriodide* (0·36 g., 66%), m. p. 185—188°, yellow prisms (Found: C, 47·6; H, 5·75; N, 3·6; I, 34·1. $C_{29}H_{37}O_4N_2I,HI$ requires C, 47·6; H, 5·2; N, 3·8; I, 34·65%), $\lambda_{max.}$ (in H_2O) 227, 240 sh, 305, 354 mμ (log ε 4·80, 4·51, 4·20, 4·18 respectively).

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide* (XXV; A).—(i) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidylacetic acid (XIII; A) (1·05 g.; m. p. 155·5—157°) was esterified with absolute ethanol (30 c.c.) and hydrogen chloride at room temperature for 18 hr. The ethanol and hydrogen chloride were removed and the resulting ester hydrochloride was cyclised in toluene (5 c.c.) by phosphorus oxychloride (3 c.c.) at 95° for 0·5 hr. The quaternary *iodide*, prepared in the usual way, was extracted with chloroform and crystallised from ethanol–ethyl acetate with a few drops of ether, as yellow needles (1·26 g., 86%), double m. p. 135—140° and 167—170° (Found: C, 51·8; H, 6·0; N, 2·9; I, 26·4. $C_{21}H_{30}O_4NI$ requires C, 51·75; H, 6·2; N, 2·9; I, 26·0%), $\lambda_{max.}$ (in H_2O) 235, 302, and 348 mμ (log ε 4·34, 4·0, and 4·1).

(ii) The hydriodide (XXVI; A) (1·2 g.) was treated in methanol (5 c.c.) with excess of 2N-sodium carbonate, and the base extracted with ether, recovered, and heated in glacial acetic acid (30 c.c.) with mercuric acetate (2·4 g.) at 60° for 2·5 hr. Mercurous acetate separated after 10 min. The solution was cooled, diluted with water, and filtered. The filtrate was treated with hydrogen sulphide, the metal sulphide was filtered off, and the filtrate concentrated to 50 c.c. and acidified with hydrochloric acid. Potassium iodide was added and the quaternary iodide ester was extracted with chloroform and crystallised from methanol–ether as yellow plates (0·94 g., 78%), m. p. and mixed m. p. 170·5—171·5°.

Similarly the acetic acid (XIII; B) (2·52 g.) gave the *ester iodide* (XXV; B) as yellow prisms (3·01 g.) (from methanol–ethyl acetate–ether), m. p. 168—170° (Found: C, 52·35; H, 6·1; N, 2·9%).

Also the quinolizine hydriodide (XXVI; B) (0·27 g.) was dehydrogenated with mercuric acetate in acetic acid to give the ester iodide (XXV; B) (0·20 g.), m. p. and mixed m. p. 168—170°.

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11b*H*-*benzo*[a]*quinolizine Hydriodide* (XXVI; A).—(i) The iodide ester (XXV; A) (0·97 g.) was hydrogenated in methanol (10 c.c.) with Adams catalyst (0·2 g.) at room temperature and atmospheric pressure. After filtration, concentration, and dilution with ether, the *hydriodide* separated as colourless needles (0·89 g., 91%), double m. p. 163—165° and 183·5—184·5° (Found: C, 51·5; H, 6·3; N, 3·0; I, 26·3. $C_{21}H_{31}O_4N,HI$ requires C, 51·5; H, 6·6; N, 2·9; I, 25·9%).

(ii) The iodide ester (XXV; A) (1·22 g.) was dissolved in methanol (40 c.c.) and saturated aqueous sodium hydrogen carbonate (40 c.c.) and treated at room temperature with sodium dithionite (4·0 g.) in two portions during 0·5 hr. The solution was left overnight, made strongly alkaline with 2N-sodium hydroxide, and extracted with ether. The hydriodide of the extracted base separated from ethanol as needles, m. p. 180—184° (1·02 g., 83%), identical with the previous preparation.

(iii) The iodide ester (1·2 g.) was treated in methanol (5 c.c.) with 2N-aqueous sodium carbonate. The anhydronium base was extracted with ether, dried (K_2CO_3), and recovered. To it was added 98% formic acid (0·17 g.) and the whole was kept at 60° for 2·25 hr., then

dissolved in 2N-hydrochloric acid. Potassium iodide was added. The hydriodide crystallised from methanol–ether as needles, m. p. and mixed m. p. 178—181° (1·0 g., 82%).

The isomeric iodide ester (XXV; B) (2·25 g.) was hydrogenated as described in (i) above. The *hydriodide* (2·17 g.) separated from methanol–ether as needles, m. p. 214·5—216·5° (Found: C, 51·8; H, 6·7; N, 2·9%).

A sample of the acid (m. p. 170—171°) corresponding to structure (XXVI) obtained from Drs. Brossi and Schnider [19] was esterified with ethanol and hydrogen chloride at room temperature; the ethyl ester was characterised as the hydriodide and crystallised from methanol–ether as needles, m. p. 214—216°. A mixed m. p. with the above sample showed no depression and infrared comparison of the two samples showed them to be identical (Found: C, 52·0; H, 6·6; N, 3·0%).

2-[N-(3,4-*Dimethoxyphenethyl*)*carbamoylmethyl*]-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine* (XXVII; A).—The ester hydriodide (XXVI; A) (2·44 g.) was hydrolysed with aqueous-alcoholic 10% potassium hydroxide (30 c.c.) at 95° for 2 hr. The alcohol was removed, the pH of the solution adjusted to pH 7, and the acid extracted with chloroform. The gummy acid was refluxed with 3,4-dimethoxyphenethylamine (1·8 g.), acetic acid (0·2 c.c.), and ammonium acetate (0·2 g.) in xylene (30 c.c.), in a Dean–Stark apparatus with separation of water, for 12 hr. The xylene was removed, water added, and the yellow solid filtered off and washed with water and ether. The *amide* separated from ethyl acetate as needles, m. p. 151·5—154·5° (1·58 g., 64%) (Found: C, 70·2; H, 8·1; N, 5·6. $C_{29}H_{40}O_5N_2$ requires C, 70·1; H, 8·1; N, 5·6%). The hydriodide had m. p. 227—228°. An amide of the same structure (XXVII; A) was later prepared by Brossi and Schnider [19] by a different route and had m. p. and mixed m. p. 152—154°; infrared comparison in Nujol showed them to be identical.

2-(3,4-*Dihydro*-6,7-*dimethoxy*-2-*isoquinolylmethyl*)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine Dihydrobromide* (XXVIII, *A*) [(±)O-*Methylpsychotrine*].—The amide (XXVII; A) (2·42 g.) was heated in benzene (40 c.c.) with phosphorus oxychloride (6 c.c.) for 0·5 hr., whereupon a red oil separated. The solvent was removed and the residue dissolved in water and basified with 2N-sodium carbonate. The base was extracted with ether (3 times) and converted into the dihydrobromide which separated from methanol–ether as yellow nodules (2·25 g., 68%), m. p. 197—204°, softens at 195° [(+)-*O*-Methylpsychotrine dihydrobromide [27] has m. p. 190—200°] (Found, in air-dried specimen: C, 51·4; H, 6·25; N, 4·4. $C_{29}H_{38}O_4N_2$,2HBr,2H_2O requires C, 51·5; H, 6·6; N, 4·1%). Drying at 100° did not remove the water of crystallisation and the same analysis was obtained.

(±)-*Emetine* (XXII; Aa_1) *and its Resolution*: *Stereoisomers* (XXII; Ab_2, Bc_1, Bd_1).—*1st Route. Reduction of stereoisomers of dehydroemetinium salts* (XXI). (i) (±)-Emetine (XXII; Aa_1). Dehydroemetinium iodide hydriodide (XXI; Aa) (1·46 g.) was converted into the chloride hydrochloride by shaking it with silver chloride in aqueous methanol, and the solution was filtered and evaporated to dryness. The residue was dissolved in methanol (20 c.c.) and hydrogenated with Adams catalyst (0·2 g.) at room temperature and atmospheric pressure. After rapid uptake of 1 mol. of hydrogen the solution was filtered and ether was added. The *dihydrochloride* (1·0 g.) of base (XXII; Aa_1) crystallised as prisms, m. p. 252—257° (sinters at 247°). A mixed m. p. with (+)-emetine dihydrochloride gave no depression. An infrared comparison in Nujol showed the two to be very similar but not identical (Found: C, 59·5; H, 7·9; N, 5·4; Cl, 12·4. $C_{29}H_{40}O_4N_2$,2HCl,2H_2O requires C, 59·1; H, 7·9; N, 4·75; Cl, 12·0%. Found, in sample dried at 100°: C, 61·9; H, 7·7; N, 5·0. $C_{29}H_{40}O_4N_2$,2HCl,0·5H_2O requires C, 61·9; H, 7·7; N, 5·0%). The dihydriodide, obtained by treatment of an aqueous solution of the dihydrochloride with sodium iodide, separated from methanol as woolly needles, m. p. 227—228°. A mixed m. p. with (+)-emetine dihydriodide (m. p. 228—229·5°; lit.,[28] m. p. 215—216°, 228—230°, 235—238°) showed no depression and a comparison of the two salts' infrared spectra showed no difference (Found in air-dried sample: C, 45·0; H, 5·6; N, 3·7; I, 32·5; H_2O, 4·3. $C_{29}H_{40}O_4N_2$,2HI,2H_2O requires C, 45·1; H, 5·7; N, 3·6; I, 32·85; H_2O, 4·9. Found, in sample dried at 100°: C, 47·3; H, 5·2; N, 3·9; I, 34·5. $C_{29}H_{40}O_4N_2$,2HI requires C, 47·2; H, 5·7; N, 3·8; I, 34·5%). The base, derived from an aqueous solution of the hydrochloride by treatment with alkali, was a colourless amorphous solid, m. p. 68—70° (meniscus at 74°). A mixed m. p. with (−)-emetine (m. p. 74°) gave no

[27] Pyman, *J.*, 1917, **111**, 419.
[28] Karrer, *Ber.*, 1916, **49**, 2065; Keller, *Arch. Pharm.*, 1911, 521; Carr and Pyman, *J.*, 1914, **105**, 1604.

depression and the infrared spectra (in CS_2) of the two were identical. The (±)-base (XXII; Aa_1) (0·5 g.) in methanol was treated with (+)-dibenzoyltartaric acid (0·57 g., 2 mol.) in methanol–ethyl acetate: ethyl acetate was then added to turbidity and the solution seeded with the authentic salt. The (−)-*emetine bisdibenzoyltartrate* slowly crystallised and after two recrystallisations from methanol–ethyl acetate had m. p. 182—182·5° (decomp.), $[\alpha]_D^{20}$ −61·4° ±0·5° (*c* 1·002 in MeOH). An authentic specimen had m. p. 180—181°, $[\alpha]_D^{20}$ −62° (*c* 1·00 in MeOH); a mixed m. p. gave no depression and the infrared spectra were identical (Found: C, 64·6; H, 6·5; N, 2·7. $C_{29}H_{40}O_4N_2,C_{36}H_{28}O_{16},H_2O$ requires C, 64·9; H, 5·9; N, 2·3%). The (−)-base, obtained from this salt, with hydrochloric acid and sodium iodide gave the (+)-dihydriodide (sparingly soluble in water), needles (from methanol–ether), m. p. 228—230° (sinters at 225°), $[\alpha]_D^{19}$ +26·25° ±1·75° (*c* 0·571 in chloroform). An authentic sample had m. p. 228—229°, $[\alpha]_D^{19}$ +22·2° ±0·9° (in chloroform) (Found, in sample dried at 100°: C, 46·5; H, 5·8; I, 33·7. Calc. for $C_{29}H_{40}O_4N_2,2HI,H_2O$: C, 46·2; H, 5·9; I, 33·65%). In addition the (+)dihydrochloride was prepared from the (−)-dibenzoyltartrate in 82% yield, as needles (from methanol–ethyl acetate–ether), m. p. 235—250°, $[\alpha]_D^{20}$ +44·85° ±0·95° (*c* 1·07 in chloroform). An authentic specimen had m. p. 235—250°, $[\alpha]_D^{23}$ +46° (in chloroform) {lit.,[29] m. p. 235—250°, $[\alpha]_D^{20}$ +55° (in chloroform)} (Found: C, 57·0; H, 8·35; N, 4·4; H_2O, 8·0. Calc. for $C_{29}H_{40}O_4N_2,2HCl,3H_2O$: C, 57·3; H, 8·0; N, 4·6; H_2O, 8·9%). A mixed m. p. between these salts and authentic samples gave no depression and the infrared spectra (in KBr) of each pair were identical.

From the mother-liquor, after removal of a further small amount of the dihydriodide of base (XXII; Aa_1), the second isomer (cf. XXII; Aa_2) was obtained only as amorphous salts. The *dihydrochloride* had m. p. 235—240° (Found: C, 60·0; H, 7·5; N, 4·9; Cl, 12·6. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9; Cl, 12·4%).

(ii) The dehydroemetinium iodide hydriodide (XXI; Ab) (1·80 g.) was converted into the chloride hydrochloride and reduced as described above. The *dihydrochloride* of base (XXII; Ab_2) crystallised readily as prisms (0·8 g.), m. p. 250—270°, softening at 240° (Found, in air-dried sample: C, 60·35; H, 8·3; N, 4·5. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9%). This stereoisomer was examined by paper chromatography by the method described below and was found to be homogeneous and readily separated from emetine.

(iii) (*a*) The amorphous dehydroemetinium iodide hydriodide (XXI; Bc) (0·8 g.) in methanol (10 c.c.) was treated portionwise with sodium borohydride (1·0 g.) at 20°. After 0·5 hr. the solvent was removed and the residue treated with 2N-sodium carbonate and benzene. The benzene extracts were washed with water, then evaporated, and the product was converted into the *dihydrochloride* of base (XXII; Bc_1). This salt crystallised from methanol–ether as colourless prisms (0·28 g.), m. p. 261—267° (sinters at 258°). It can be separated readily from emetine by paper chromatography in the usual solvent system, and gave only one spot (Found, in air-dried sample: C, 59·3; H, 7·7; N, 4·8; Cl, 12·1. $C_{29}H_{40}O_4N_2,2HCl,2H_2O$ requires C, 59·1; H, 7·9; N, 4·75; Cl, 12·0%). The other epimer was not obtained. Comparison with an emetine isomer prepared by Drs. Brossi and Schnider [19] by m. p., mixed m. p., paper chromatography, toxicity, amœbicidal evaluation *in vivo*, and infrared spectroscopy showed them to be identical.

(*b*) The amorphous dehydroemetinium iodide hydriodide (XXI; Bc) (2·0 g.) was converted into the chloride hydrochloride in water and methanol with silver chloride (from 0·25 g. of silver nitrate) and hydrogenated in methanol (30 c.c.) with platinum oxide (0·18 g.). The solution was filtered, concentrated and diluted with ether and hydrochloric acid (0·1 c.c.). The dihydrochloride of base (XXII; Bc_1) separated as prisms (0·8 g.), m. p. 267—274° (decomp.), identical with the above specimen on paper chromatography.

(iv) Dehydroemetinium iodide hydriodide (XXI; Bd) (0·75 g.) was treated in methanol (15 c.c.) with potassium borohydride (0·3 g.) at 0°. The product was isolated after 1 hr. at 20° as the *dihydrochloride* of base (XXII; Bd), prisms (0·17 g.) (from methanol–ether), m. p. 215—220° (Found, in air-dried sample: C, 55·0; H, 7·8; N, 4·5; Cl, 11·9; loss on drying at 100°, 8·1. $C_{29}H_{40}O_4N_2,2HCl,4{\cdot}5H_2O$ requires C, 54·8; H, 8·1; N, 4·4; Cl, 11·1; $3H_2O$, 6·75. Found, in sample dried at 100°: C, 60·0; H, 7·6; N, 4·9. $C_{29}H_{40}O_4N_2,2HCl,1{\cdot}5H_2O$ requires C, 60·0; H, 7·8; N, 4·8%). Paper chromatography gave a single spot, easily separated from that of the salts of emetine and (XXII; Bc_1). This isomer (Bd_1) was also obtained by Drs. Brossi and Schnider [19] and m. p., mixed m. p., infrared spectroscopy, and paper chromatography showed them to be identical.

[29] Pyman, *J.*, 1914, **105**, 1591.

2nd Route. From stereoisomers of tetradehydroemetinium salts (XXIII). (i) *Salts of bases* (XXII; Ab_2 *and* Aa_1). Tetradehydroemetinium iodide hydriodide (XXIII; A_1) (2·07 g.) was shaken in hot water (75 c.c.) with silver chloride (from silver nitrate, 2 g.). The resulting chloride hydrochloride in methanol (20 c.c.) was reduced catalytically with platinum oxide (0·1 g.) at room temperature and pressure. After two mols. of hydrogen had been taken up the solution was filtered, concentrated, and diluted with ether. The *dihydrochloride* of base (XXII; Ab_2) separated as prisms (1·0 g., 60%), m. p. 245—260°, sinters 235°. Paper chromatography gave a single spot identical with that of isomer (Ab_2) obtained as described above. This identity was confirmed by the amœbicidal activity (Found: C, 60·43; H, 7·75; N, 4·6; Cl, 12·2. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9; Cl, 12·4%). The mother-liquor yielded on concentration two small further crops of dihydrochlorides which were mixtures (XXII; Aa_1 and Ab_2). Unfortunately (Aa_1) was present in only very small amounts and could not be purified.

Sodium borohydride reduction in methanol gave isomer (Ab_2) in 50% yield.

(ii) *Salt of base* (XXII; Bc_1). The tetradehydroemetinium iodide hydriodide (XXIII; B) (0·5 g.) was converted into the chloride hydrochloride and hydrogenated in methanol (25 c.c.) with platinum oxide (0·1 g.). The dihydrochloride produced crystallised as prisms (0·15 g.), m. p. 255—265°, and had the same R_F value as (XXII; Bc_1) with which on this basis it was considered to be identical.

3rd Route. From (±)-O-*methylpsychotrine* (XXVIII; A). *Salts of bases* (XXII; Aa_1 *and* Ab_2). (±)-*O*-Methylpsychotrine dihydrobromide (XXVIII; A) (2·25 g.) was hydrogenated (1 mol.) in methanol (50 c.c.) with Adams catalyst (0·2 g.). The solution was then warmed and filtered. The alcohol was removed, water and 2N-sodium carbonate were added, and the base was extracted with ether and converted into mixed dihydrochlorides. Crystallisation from methanol–ether gave the dihydrochloride of base (XXII; Ab_2) as needles (0·88 g., 45%), m. p. 249—263° (Found, in sample dried at 100°: C, 62·1; H, 7·8; N, 5·0. $C_{29}H_{40}O_4N_2,2HCl,0·5H_2O$ requires C, 61·9; H, 7·7; N, 5·0%). This isomer was identified as Ab_2 by its R_F value and mixed m. p. Concentration of the mother-liquor and addition of ether gave the dihydrochloride (0·84 g.), m. p. and mixed m. p. 247—257°, of base (XXII; Aa_1) (Found, in sample dried at 100°: C, 61·9; H, 7·65; N, 5·0%). Isomer (Aa_1) [(±)-emetine] was more difficult to free from traces of (Ab_2), as shown by paper chromatography, and three crystallisations were necessary to obtain a homogeneous sample, but the R_F of the final sample was the same as that of Aa_1 and emetine.

Paper Chromatography of Emetine Stereoisomers.—Ethyl methyl ketone (600 c.c.) was shaken with 2N-hydrochloric acid (200 c.c.). The ketone layer was used as the eluant in descending chromatography. Emetine dihydrochloride was used as a marker spot and given R_F 1 (distance travelled = 31 cm.). The R_F values are given in Table 1; in addition to the isomers (Ab_2, Bc_1, and Bd_1) in Table 1 which could be separated from emetine it was possible to separate isomers (Bc_1) and (Bd_1). The spots were detected with a reagent described by Brossi, Hafliger, and Schnider.[30]

(±)-*Rubremetinium Bromide* (XXIV).—Tetradehydroemetinium iodide hydriodide (XXIII; A) (0·37 g.) was oxidised in dilute acetic acid containing potassium acetate and mercuric acetate according to the procedure of Battersby, Openshaw, and Wood.[4] The bromide crystallised from dilute hydrobromic acid as orange-red needles (0·16 g.). When dried at 50° *in vacuo* for 1·5 hr. the salt had m. p. 177—185° with the meniscus at 197—205°, behaviour similar to natural (+)-rubremetinium bromide (Pyman [29] records m. p. 160—180°, meniscus at 195—205°) (Found, in air-dried specimen: C, 58·3; H, 6·2; N, 4·7. Calc. for $C_{29}H_{33}O_4N_2Br,2·5H_2O$: C, 58·2; H, 6·4; N, 4·7%. Found, in sample dried at 100°: C, 62·2; H, 5·9; Br, 14·9. Calc. for $C_{29}H_{33}O_4N_2Br$: C, 62·9; H, 6·0; Br, 14·4%). The (±)-salt had $\lambda_{max.}$ (in H_2O) 257·5, 288, 300, 437·5 mμ (log ε 4·21, 4·22, 4·22, 4·44). (+)-Rubremetinium bromide had $\lambda_{max.}$ (in H_2O) 257·5, 288, 300, 437·5 mμ (log ε 4·21, 4·20, 4·21, 4·40). The infrared spectra (hexachloroethane KBr, Nujol) and the R_F (butanol, acetic acid, and water) were the same.

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Welwyn Garden City, Herts. [*Received, April 21st,* 1959.]

[30] Brossi, Hafliger, and Schnider, *Arzneimittel-Forsch.*, 1955, **5**, 62.