277. *The Synthesis of Emetine and Related Compounds. Part V.* A Stereochemically Favourable Synthesis of Emetine.*

By H. T. Openshaw and Norman Whittaker.

An efficient synthesis of (−)-emetine (XIV) has been developed. When heated with (−)-camphor-10-sulphonic acid in ethyl acetate, the racemic keto-base (I) is converted almost completely into the (−)-isomer. Treatment of this with methoxycarbonylmethylenetriphenylphosphorane (II) gives the (+)-αβ-unsaturated ester (III) which on hydrogenation gives over 70% of the desired (−)-2,3-*trans*-product (Va), converted by known methods into (+)-*O*-methylpsychotrine (XIII). Reduction of (+)-*O*-methylpsychotrine gives a mixture of emetine and isoemetine, but the latter, unwanted isomer can be almost quantitatively reconverted into (+)-*O*-methylpsychotrine by *N*-chlorination followed by alkali treatment.

Other methods investigated (using the racemic compound) for the conversion of the ketone (I) into the unsaturated ester (III) led instead to stereoisomeric products (*e.g.*, VIII), unsuitable as intermediates for emetine. Correlation of these results permits a rigid allocation of configurations (VIb and IXb) to the two previously described stereoisomers of the 3,4-dimethoxyphenethylamide (Vb).

In Part IV, a convenient synthesis of the 2-oxobenzo[*a*]quinolizine (I) was described. From this racemic compound we have now developed a stereochemically favourable synthesis of the optically active alkaloid emetine (XIV).†

The emetine molecule (XIV) contains four centres of asymmetry, the relative and absolute orientations of which have been established, largely by the work of Battersby and his co-workers.[1] Three of the asymmetric centres occur in the benzo[*a*]quinolizine portion of the molecule, and their configurations are those expected to be the most stable, since they permit of an equatorial configuration for the largest substituent at each centre. The ketone (I) already contains two of the asymmetric centres, but only one racemate has been obtained. This is thought to possess the desired, most stable configuration,[2] and is therefore a promising starting point for a stereospecific synthesis. The initial step was to obtain the unsaturated ester (III) by a Wittig reaction. Phosphoranes such as (II) are comparatively unreactive [3] towards ketones, but recently it has been shown by Fodor and Tömösközi,[4] and the present authors,[5] that the use of elevated reaction temperatures gives satisfactory yields of the expected products. When the ketone (I) was heated with an excess of the phosphorane (II) in xylene under reflux, or at 150° in the absence of solvent, a 58% yield of the αβ-unsaturated ester (III) was obtained. It gave the corresponding carboxylic acid on hydrolysis with aqueous acid, but reaction of the ester with 3,4-dimethoxyphenethylamine was accompanied by migration of the ethylenic bond into the ring, giving the 3,4-dimethoxyphenethylamide (IVb). Since this amide, on hydrogenation, gives mainly 2,3-*cis*-isomers,[6] it is unsuitable as an intermediate for the synthesis of emetine. In contrast, catalytic hydrogenation of the ester (III) in methanolic hydrogen chloride in the presence of platinum gave a preponderance of the desired crystalline

* Part IV, preceding paper.

† In this paper, where compounds are optically active, the formulæ depict their absolute configurations; for racemic compounds, only one enantiomer is represented, except in the case of formula (IX) where both are shown.

[1] Battersby, Binks, and Davidson, *J.*, 1959, 2704; Battersby and Garratt, *J.*, 1959, 3512.

[2] Battersby, Binks, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982; Brossi, Lindlar, Walter, and Schnider, *Helv. Chim. Acta*, 1958, **41**, 119.

[3] Sugasawa and Matsuo, *Chem. and Pharm. Bull.*, 1960, **8**, 819; Trippett and Walker, *Chem. and Ind.*, 1961, 990.

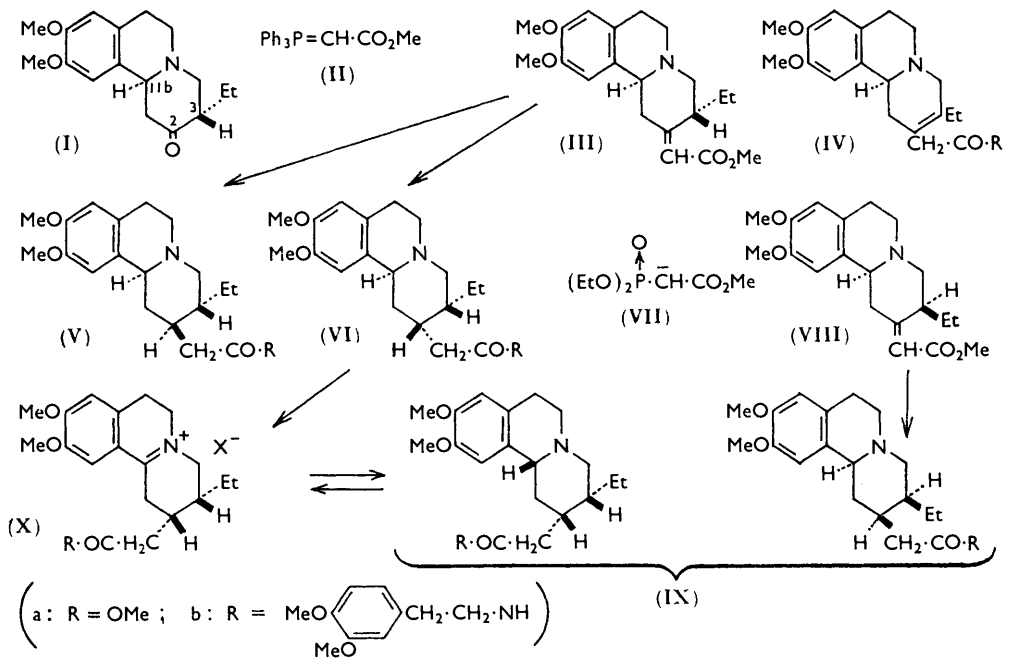
[4] Fodor and Tömösközi, *Tetrahedron Letters*, 1961, 579.

[5] Openshaw and Whittaker, *Proc. Chem. Soc.*, 1961, 454.

[6] Brossi, Baumann, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 1515.

2,3-*trans*-ester (Va), together with the isomer (VIa). With palladium, in place of platinum, a 74% yield of the 2,3-*trans*-ester was obtained. The stereochemical configuration of this ester was confirmed by its conversion, through the 3,4-dimethoxyphenethylamide (Vb), into (±)-*O*-methylpsychotrine,[7] which was resolved to give (+)-*O*-methylpsychotrine (XIII) identical with the natural alkaloid.

Phosphonate carbanions have recently been reported [8,9] to be highly reactive towards ketones, and so the reaction of the carbanion (VII) with the ketone (I) was also investigated. Reaction occurred even at room temperature but the composition of the product was dependent on the procedure. When the carbanion (VII) was formed by means of sodium hydride in 1,2-dimethoxyethane, a mixture of two new αβ-unsaturated esters resulted which were *cis–trans*-isomers with respect to the ethylenic bond, for on catalytic hydro-



genation they gave the same saturated ester. The latter was not identical with either of the esters (Va) and (VIa), and therefore stereochemical inversion at C-3 had occurred in the phosphonate reaction, and the *cis–trans*-isomers must have the structure (VIII). The product of their reduction was shown to be the 2,3-*cis*-ester (IXa) for both it and the ester (VIa), whose 2,3-*cis*-configuration follows from its relationship to the isomer (Va), are dehydrogenated to the same benzo[*a*]quinolizinium salt (Xa). Hydrogenation of this salt gives only the isomer (IXa). The structural assignment was confirmed by similar conversion of the 3,4-dimethoxyphenethylamide (VIb) into the isomer (IXb).* When the carbanion (VII) was generated by use of sodium methoxide in methanol, it reacted with the ketone (I) to give a mixture of the *cis*- and *trans*-esters (VIII) with the ester (III). This suggests that the extent of the epimerisation at C-3 depends on the strength of the

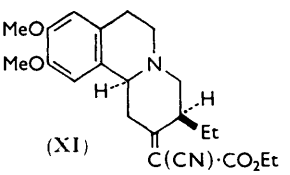
* Brossi and Schnider [10] have independently established the configurations shown for the 3,4-dimethoxyphenethylamides (VIb) and (IXb). We are grateful to Dr. A. Brossi for informing us of their results in advance of publication.

[7] Battersby and Turner, *J.*, 1960, 717.
[8] Emmons and Wadsworth, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.
[9] Pommer, *Angew. Chem.*, 1960, **72**, 811, 911.

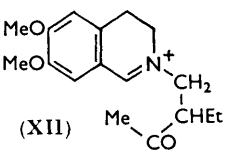
base used to bring about the reaction. In the presence of weaker bases, such as tri-n-butylamine or piperidine, or when the ketone (I) and phosphonate were heated together at 150—160°, no reaction occurred.

Brossi and Schnider [10] have described the condensation of the ketone (I) with ethyl cyanoacetate and the conversion of the product by successive reduction, hydrolysis, and reaction with 3,4-dimethoxyphenethylamine into a 3,4-dimethoxyphenethylamide from which they derived isomers of emetine and isoemetine. We have repeated their work and find that the 3,4-dimethoxyphenethylamide produced is identical with that (IXb) obtained by the above phosphonate route. Thus, the reaction of the ketone (I) with ethyl cyanoacetate is also accompanied by stereochemical inversion at C-3, and the product can now be formulated as (XI).

Although (±)-*O*-methylpsychotrine is obtained from the ketone (I) in satisfactory yield, and an efficient resolution has been described,[7] it is obviously wasteful to resolve the material at so late a stage in the synthesis, where the unwanted (—)-*O*-methylpsychotrine is discarded. Resolution at an earlier stage seemed desirable and so the resolution of the ketone (I) was attempted in the hope that the unwanted enantiomer could be racemised and used further. In fact, an even more useful result was obtained. When a solution of

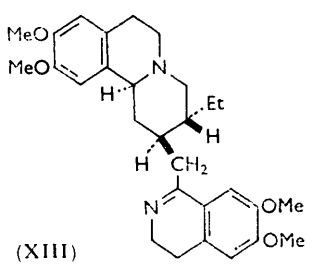


(XI)

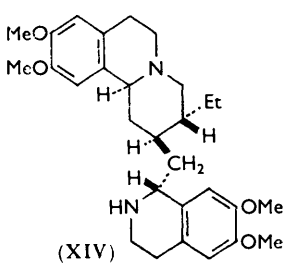


(XII)

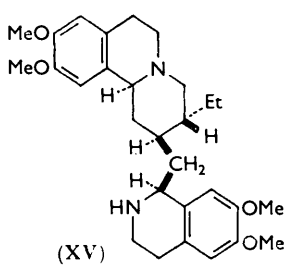
the ketone (I) and (+)-camphor-10-sulphonic acid in ethyl acetate was set aside at room temperature, partial resolution occurred, for the resulting salt gave an optically active base. This gave a base of higher optical rotation when the process was repeated. When the ketone (I) was heated with (+)-camphor-10-sulphonic acid in ethyl acetate under reflux, however, larger yields of optically purer base resulted. The yield increased with longer periods of refluxing and, after 22½ hours, 80% of the original racemate was obtained as the pure (+)-ketone. It was therefore apparent that as the salt of the (+)-enantiomer crystallised the desired racemisation of the (—)-enantiomer was simultaneously occurring in the solution. Racemisation is probably due to an interconversion of the benzo[*a*]quinolizine (I) and the isoquinolinium structure (XII) in the presence of acid, together with



(XIII)



(XIV)



(XV)

epimerisation at C-3.* In support of this it has been shown that the (+)-benzo[*a*]quinolizine undergoes slow racemisation on being heated with acid. Reaction of the (+)-ketone with the phosphorane (II) proceeded without racemisation, giving a (—)-αβ-unsaturated ester, and this on catalytic hydrogenation yielded a dextrorotatory saturated ester. The

* This is believed to be the first example of a " second-order " asymmetric transformation [11] involving the simultaneous inversion of two dissimilar asymmetric centres.

[10] Brossi and Schnider, *Helv. Chim. Acta*, 1962, **45**, 1899; B.P., 798,847.

[11] Harris, " Progress in Stereochemistry," Vol. II, ed. Klyne and de la Mare, Butterworths Scientific Publ., London, 1958, p. 158.

ester of the absolute configuration (Va) is lævorotatory,[12] however, and so it was apparent that the required ketone, of absolute configuration shown in formula (I), is the (—)-enantiomer. This was obtained in 85% yield from the racemic compound by prolonged heating with (—)-camphor-10-sulphonic acid in ethyl acetate, and was converted through the (+)-αβ-unsaturated ester (III) into the (—)-saturated ester (Va). The derived 3,4-dimethoxyphenethylamide was then cyclised by phosphoryl chloride to give (+)-*O*-methylpsychotrine (XIII), identical with the natural alkaloid.

Catalytic hydrogenation of (+)-*O*-methylpsychotrine (XIII) gives a mixture of emetine (XIV) with isoemetine (XV). Reduction of the hydrogen oxalate is reported[13] to give only isoemetine, whilst reduction of the base in ethanol gives[7] a slight preponderance of emetine. We have examined by chromatography the composition of the product resulting from several reduction procedures. Catalytic hydrogenation of (+)-*O*-methylpsychotrine with platinum in methanolic sodium methoxide gave a slight increase in the proportion of emetine, whilst in aqueous solution at pH *ca.* 5 the ratio of emetine to isoemetine was 1 : 3·5. Reduction by means of lithium aluminium hydride in ether, or by potassium borohydride in methanol, gave approximately equal amounts of the isomers.

In the synthesis of emetine outlined above, the reduction of the (+)-*O*-methylpsychotrine is the least stereospecific step. Conversion of the unwanted isoemetine back into (+)-*O*-methylpsychotrine was therefore desirable, in order that this might be reduced again to provide more emetine. Catalytic dehydrogenation of isoemetine by palladised charcoal in, for example, mesitylene solution at 180° gave some (+)-*O*-methylpsychotrine. The incorporation of hydrogen acceptors led to improved yields but the maximum, when nitrobenzene was the acceptor, was only 39%. Oxidation of isoemetine with chloranil gave 25% of (+)-*O*-methylpsychotrine but argentic picolinate[14] gave none. Reaction of isoemetine with a *N*-chlorinating agent, followed by dehydrochlorination of the resulting *N*-chloroisoemetine with alkali, proved to be the method of choice; with *N*-chlorosuccinimide or aqueous sodium hypochlorite, the yield of (+)-*O*-methylpsychotrine was 90—92%. A similar result was obtained when the method was applied to emetine. Accordingly, after isolation of emetine dihydrobromide from the product of reduction of (+)-*O*-methylpsychotrine, the isoemetine and residual emetine present in the liquors may be converted back into (+)-*O*-methylpsychotrine, resulting in an overall yield of emetine of *ca.* 80%.

The hypochlorite oxidation can also be applied in the dehydroemetine series. Reduction of (±)-2-dehydro-*O*-methylpsychotrine gives[15] a mixture of (±)-2-dehydroemetine with (±)-2-dehydroisoemetine, and the latter can be smoothly reconverted into (±)-2-dehydro-*O*-methylpsychotrine. Other 1,2,3,4-tetrahydroisoquinolines can similarly be converted into 3,4-dihydroisoquinolines.

Experimental

Ultraviolet spectra were determined with a Hilger Uvispek instrument. Infrared spectra were measured for potassium chloride dispersions, by means of a Unicam S.P. 100 spectrophotometer with grating accessory.

3-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-2-methoxycarbonylmethylene-11bH-benzo[a]*quinolizine* (III).—(*a*) An intimate mixture of the 2-oxobenzo[*a*]quinolizine (I) (40 g.) with the phosphorane[16] (II) (69·5 g., 1·5 mol.) was heated in a bath at 161° under dry nitrogen, and the resulting liquid was maintained at 152° for 3 hr. The cooled reaction product was treated with hot benzene (250 ml.) and freshly distilled benzaldehyde (29·4 g., 2 mol.), the mixture was refluxed for 1 hr., and the cooled benzene solution was extracted with water (400 ml.) plus

[12] Battersby and Harper, *J.*, 1959, 1748.
[13] Karrer, Eugster, and Rüttner, *Helv. Chim. Acta*, 1948, **31**, 1219.
[14] Bacon and Hanna, *Proc. Chem. Soc.*, 1959, 305; Bacon, *Chem. and Ind.*, 1962, 19.
[15] Brossi, Baumann, Chopard-dit-Jean, Würsch, Schneider, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 772.
[16] Isler, Gutmann, Montavon, Rüegg, Ryser, and Zeller, *Helv. Chim. Acta*, 1957, **40**, 1242.

sufficient N-hydrochloric acid (*ca.* 150 ml.) to give an acidic extract. The aqueous extract was washed with benzene and basified with aqueous potassium hydroxide, the precipitated base was extracted with chloroform (2 × 200 ml.), and the chloroform solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was freed from traces of chloroform by distillation with light petroleum (b. p. 60—80°), and a solution of the resulting solid in hot light petroleum (b. p. 60—80°) (*ca.* 150 ml.) was filtered from resin and evaporated. Crystallisation of the residual solid from methanol (80 ml.), with cooling to 0°, gave the unsaturated *ester* (III) (25·6 g., 54%), m. p. 110—111°, raised by recrystallisation from methanol to 112—113° (Found: C, 69·5; H, 7·75; N, 4·05. $C_{20}H_{27}NO_4$ requires C, 69·55; H, 7·9; N, 4·05%), $\lambda_{max.}$ (in MeOH) 232 (infl.) and 282 mμ (ε 13,200 and 4660), $\nu_{max.}$ 1717 (C=O, conjugated) and 1640 $cm.^{-1}$ (C=C, conjugated). The *perchlorate*, crystallised from methanol, had m. p. 220—221° (Found: C, 54·15; H, 6·5; N, 3·25; Cl, 7·95. $C_{20}H_{28}ClNO_8$ requires C, 53·9; H 6·35; N, 3·15; Cl, 7·95%), $\nu_{max.}$ 1704 (C=O, conjugated) and 1650 $cm.^{-1}$ (C=C, conjugated).

(*b*) A solution of the 2-oxobenzo[*a*]quinolizine (I) (48 g.) and the phosphorane (II) (124·9 g., 2·25 mol.) in hot xylene (234 ml.) was heated until 70 ml. of xylene had distilled, then refluxed under dry nitrogen for 6 hr., yielding the unsaturated ester (III) (33·4 g., 58%), m. p. 109—111°. Examination of the material from the liquors by chromatography on alumina failed to reveal the presence of isomers of this product.

Reactions of the Ester (III).—(a) *Hydrolysis.* The ester (III) (7·5 g.) and 2N-hydrochloric acid (100 ml.) were refluxed for 1 hr., the solution was set aside, and the resulting hydrated crystals were collected and dried at 65°, then at 90°, giving the anhydrous αβ-unsaturated *carboxylic acid hydrochloride* (7·5 g.), which formed a glass at *ca.* 142—146° (Found, after equilibration in air: N, 3·5; Cl, 9·2; loss on drying, 5·0. $C_{19}H_{26}ClNO_4,H_2O$ requires N, 3·65; Cl, 9·2; H_2O, 4·7%), $\nu_{max.}$ 1707 (C=O, conjugated) and 1655 $cm.^{-1}$ (C=C, conjugated).

(b) *Reaction with 3,4-dimethoxyphenethylamine.* The ester (III) (0·5 g.) and 3,4-dimethoxyphenethylamine (0·63 g., 2·4 mol.) were heated together under nitrogen at 180° for 3 hr., the cooled reaction product was shaken with water and set aside, and the resulting mixture of crystals and gum was shaken with more water and ether, giving crystals (0·32 g.), m. p. 146—148°. Recrystallisation from ethyl acetate gave fine needles (0·18 g.) of the dimethoxyphenethylamide (IVb), m. p. 152—153°, undepressed by authentic material [15] (Found: C, 70·65; H, 7·7; N, 5·85. Calc. for $C_{29}H_{38}N_2O_5$: C, 70·4; H, 7·75; N, 5·65%).

(c) *Hydrogenation.* The unsaturated ester (III) (15 g.) was dissolved in methanol (120 ml.) containing a slight excess of hydrogen chloride and shaken with platinum oxide (0·75 g.) under hydrogen; 1225 ml. (23°/761 mm.) was absorbed during 27 min. The filtered solution was evaporated *in vacuo*, and a solution of the residue in water was basified with aqueous potassium hydroxide and extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated, and the residual base was freed from traces of ether by distillation with petroleum (b. p. 40—60°). Crystallisation from petroleum (b. p. 60—80°) (30 ml.) gave colourless needles (7·7 g., 51%), m. p. 79—81°, of the saturated ester (Va). A recrystallised analytical sample had m. p. 79·5—82° [lit.,[17] 78·9—79·2°, and 79—98° (dimorphous)] (Found: C, 68·85; H, 8·5; N, 4·1. Calc. for $C_{20}H_{29}NO_4$: C, 69·15; H, 8·4; N, 4·05%). The perchlorate (from methanol) had m. p. 192—193° (lit.,[18] 188—188·5°) (Found: N, 3·25; Cl, 8·1. Calc. for $C_{20}H_{30}ClNO_8$: N, 3·15; Cl, 7·95%). The residue from the petroleum liquors was chromatographed on alumina, yielding a further small quantity of the crystalline base (Va), and also the isomer (VIa) as a gum.

Catalytic hydrogenation of the unsaturated ester (III) (3 g.) in methanolic hydrogen chloride (30 ml.), in the presence of 10% palladised charcoal (4 g.) in place of platinum, gave 2·23 g. (74%), m. p. 78—81°, of the ester (Va). The residue from the crystallisation liquors contained some of the isomer (VIa), for reaction with 3,4-dimethoxyphenethylamine yielded the 3,4-dimethoxyphenethylamide (VIb) (0·16 g.) together with the isomer (Vb) (0·21 g.).

Conversion of the Esters (Va) *and* (VIa) *into the 3,4-Dimethoxyphenethylamides* (Vb) *and* (VIb).—The ester (Va) (3·73 g.) and 3,4-dimethoxyphenethylamine (4·67 g.) were heated together under nitrogen at 180° for 3 hr., and the resulting cooled gum was shaken with petroleum (b. p. 60—80°) (50 ml.), ether (50 ml.), and water (300 ml.), until the gum had been completely converted into solid. The solid (4·17 g.), m. p. 146—150°, was collected, washed with water, and recrystallised by concentrating its solution in hot ethyl acetate, giving colourless

[17] van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1959, **81**, 6214.
[18] Battersby, B.P., 895,910.

needles (3·95 g.), m. p. 149·5—151·5° (lit.,[7,17] 146—148°, 150—153°), of the 3,4-dimethoxyphenethylamide (Vb) (Found: C, 69·9; H, 7·9; N, 5·55. Calc. for $C_{29}H_{40}N_2O_5$: C, 70·15; H, 8·1; N, 5·65%).

Similarly the crude ester (VIa) gave the 3,4-*dimethoxyphenethylamide* (VIb), plates (from ethyl acetate), m. p. 131—132° (Found: C, 70·45; H, 8·0; N, 5·45%).

(+)- *and* (−)-O-*Methylpsychotrine*.—The following procedure differs in detail from that of Battersby and Turner.[7]

(*a*) *Cyclisation of the* 3,4-*dimethoxyphenethylamide* (Vb). The compound (Vb) (5 g.), dry benzene (100 ml.), and phosphoryl chloride (2·5 ml.) were refluxed together for 1 hr. and cooled, and the benzene was evaporated *in vacuo*. The residual gum was shaken with chloroform and aqueous potassium hydroxide, and the chloroform solution of base was washed with water, dried (Na_2SO_4), and evaporated. A solution of the residue in alcohol was treated with an excess of alcoholic oxalic acid dihydrate, giving racemic *O*-methylpsychotrine di(hydrogen oxalate) (5·14 g.), m. p. 161—162° (effervescence) (Found, on dried material: C, 60·55; H, 6·65; N, 4·2. Calc. for $C_{33}H_{42}N_2O_{12}$: C, 60·2; H, 6·45; N, 4·25%).

(*b*) *Resolution of racemic* O-*methylpsychotrine*. Hot ethanolic solutions of the base derived from the above di(hydrogen oxalate), and of (−)-*OO*-dibenzoyltartaric acid (6·8 g.) were mixed, and the combined solution (260 ml.) was seeded with crystals of product [obtained from natural (+)-*O*-methylpsychotrine] and set aside. The resulting crystals were collected, suspended in more hot ethanol, cooled, and collected again, giving (+)-O-*methylpsychotrine di*[*hydrogen* (−)-OO-*dibenzoyltartrate*] (4·32 g.), m. p. 162—163° (effervescence), $[\alpha]_D^{21}$ −58·5° (*c* 2 in 4 : 1 MeOH–H_2O) (Found: C, 64·75; H, 5·75; N, 2·3. $C_{65}H_{66}N_2O_{20}$ requires C, 65·35; H, 5·55; N, 2·35%). The derived (+)-*O*-methylpsychotrine base (XIII), m. p. 120—123°, raised by recrystallisation from dry ether to 122—124° (Found: C, 72·9; H, 7·75; N, 5·8. Calc. for $C_{29}H_{38}N_2O_4$: C, 72·75; H, 8·0; N, 5·85%), was identical (mixed m. p., infrared spectrum) with the natural alkaloid. Treatment of the alcoholic liquors with oxalic acid dihydrate (10 g.) in ethanol gave crystals (2·3 g.), m. p. 161—162° (effervescence), which were recrystallised from methanol, yielding colourless needles of solvated (1·5 mol. of methanol) (−)-*O*-methylpsychotrine di(hydrogen oxalate) (1·99 g.), m. p. 161—162° (effervescence), $[\alpha]_D^{27}$ −42° (*c* 2 in H_2O) (Found, on dried material: C, 59·8; H, 6·6; N, 4·3%). The derived (−)-*O*-methylpsychotrine base had m. p. 122·5—124·5° (Found: C, 72·7; H, 7·95; N, 5·6%), depressed to 108—122° by the (+)-enantiomer, with which it was identical in infrared spectrum.

Reaction of the 2-*Oxobenzo*[a]*quinolizine* (I) *with the Carbanion* (VII).—(*a*) A solution of the carbanion was prepared by the dropwise addition of diethyl methoxycarbonylmethylphosphonate [19] (24 g.) to a stirred suspension of sodium hydride (50% oil-dispersion, 5·49 g.) in dry 1,2-dimethoxyethane (60 ml.) at 0° under nitrogen. After addition of the 2-oxobenzo[*a*]quinolizine (I) (30 g.) and 1,2-dimethoxyethane (15 ml.), the stirred suspension was allowed to come to room temperature. Complete dissolution resulted after *ca.* 1 hr., and was followed by the crystallisation of sodium diethyl phosphate. After 15 hr., the reaction mixture was treated with water and evaporated *in vacuo*, the residual gum was shaken with water (300 ml.) and benzene (375 ml.), and the filtered ("Hyflo") benzene solution of base was washed with water and extracted with a slight excess of 0·25N-hydrochloric acid (*ca.* 425 ml.). The aqueous extract was washed with benzene, cooled to 0°, basified with aqueous potassium hydroxide, and extracted with ether. The oily base (34 g.) recovered from the ethereal solution crystallised from petroleum (b. p. 60—80°) (50 ml.), and the resulting crystals (9·14 g.), m. p. 112—115°, were recrystallised from methanol (70 ml.), giving colourless prisms (7·8 g.), m. p. 114·5—116·5°, of an αβ-*unsaturated ester* (VIII). A further recrystallisation from petroleum raised the m. p. to 116—117·5° (Found: C, 69·9; H, 7·8; N, 4·05. $C_{20}H_{27}NO_4$ requires C, 69·55; H, 7·9; N, 4·05%), and the product had $\nu_{max.}$ 1720 (C=O, conjugated) and 1652 cm.$^{-1}$ (C=C, conjugated). It depressed the m. p. of the isomeric ester (III) and gave a perchlorate of m. p. 199—201°. The material recovered from the petroleum liquors was dissolved in methanol (100 ml.) and neutralised with 60% aqueous perchloric acid, yielding a mixture of perchlorates (23·6 g.), m. p. 180—220°. The derived mixture of bases was separated by successive elution from activated alumina with petroleum (b. p. 60—80°), benzene, and ether. Crystallisation of the early fractions from petroleum gave colourless prisms (5·6 g.), m. p. 87—89°, of a further αβ-*unsaturated ester* (VIII). A recrystallised sample had m. p. 88·5—90° (Found: C, 69·4; H, 7·65; N, 4·0%), $\nu_{max.}$ 1719 (C=O, conjugated) and 1643 cm.$^{-1}$ (C=C, conjugated), and gave a

[19] Stilz and Pommer, French P. 1,237,623.

perchlorate, m. p. 241—243°. Succeeding fractions gave first a mixture, and then a further quantity (2·84 g.) of the ester, m. p. 116—117·5°.

(*b*) A suspension of the 2-oxobenzo[*a*]quinolizine (I) (15 g.) in diethyl methoxycarbonylmethylphosphonate (12 g.), and methanol (25 ml.), stirred under nitrogen, was treated with a solution of sodium (1·31 g.) in methanol (9·5 ml.) during 5 min., with ice-cooling. The mixture was allowed to come to room temperature, with continued stirring, and after 70 min. the resulting solution was set aside overnight. The derived mixture of bases was subjected to fractional elution from activated alumina in the manner of (*a*) above, and the product of each fraction was crystallised from petroleum (b. p. 60—80°) or from methanol. The following αβ-unsaturated esters were obtained, in order of elution: (1) the lower-melting ester (VIII) (0·59 g., m. p. 87—89°); (2) the higher-melting ester (VIII) (2·7 g., m. p. 114—117°); (3) the ester (III) (3·8 g., m. p. 111—112·5°). The separation described was only semiquantitative, intermediate mixed fractions being also obtained.

Hydrogenation of the cis–trans-*Unsaturated Esters* (VIII).—A solution of the higher-melting isomer (VIII) (1 g.) in methanol (12 ml.) containing a slight excess of hydrogen chloride was shaken with platinum oxide (0·05 g.) under hydrogen, absorbing 81·5 ml. (21°/759 mm.) during 20 min. Evaporation of the filtered solution gave the hydrochloride (1·1 g.), m. p. 223—224° (effervescence), which was converted into the *perchlorate* of the saturated ester (IXa), plates (from methanol), m. p. 210—212° (Found: C, 53·45; H, 6·55; N, 3·05; Cl, 7·9. $C_{20}H_{30}ClNO_8$ requires C, 53·65; H, 6·7; N, 3·15; Cl, 7·95%), $\nu_{max.}$ 1731 cm.$^{-1}$ (C=O). An identical product (m. p., infrared spectrum) resulted from hydrogenation of the lower-melting isomer (VIII).

In a further experiment the base derived from the reduction of the higher-melting isomer (VIII) (1 g.) crystallised at 0°. After addition of petroleum (b. p. 60—80°) (1 ml.) the crystals (0·86 g.) were collected and recrystallised from petroleum (b. p. 60—80°), giving colourless prisms (0·74 g.) of the saturated *ester* (IXa), m. p. 76—78°, raised by further crystallisation to 78—79·5° (Found: C, 69·2; H, 8·25; N, 3·95. $C_{20}H_{29}NO_4$ requires C, 69·15; H, 8·4; N, 4·05%). The same ester was obtained more conveniently by hydrogenation of the mixture of isomers produced directly from the phosphonate reaction.

The 3,4-*dimethoxyphenethylamide* (IXb) was obtained as colourless small plates, m. p. 158—159° (Found: C, 70·2; H, 7·9; N, 5·5. $C_{29}H_{40}N_2O_5$ requires C, 70·15; H, 8·1; N, 5·65%), by heating the ester (IXa) with 3,4-dimethoxyphenethylamine under nitrogen at 190° for 2 hr. An identical amide (mixed m. p., infrared spectrum) was derived from the cyano-ester (XI) by successive hydrogenation, hydrolysis, and heating with 3,4-dimethoxyphenethylamine as described by Brossi and his co-workers.[10]

Correlation of Stereochemical Configurations.—(*a*) *The esters* (IXa) *and* (VIa). A solution of the ester (IXa) (3 g.) and mercuric acetate (8·8 g.) in 10% aqueous acetic acid (75 ml.) was refluxed for 50 min. The cooled reaction mixture was diluted with aqueous acetic acid and saturated with hydrogen sulphide, and the filtered (" Hyflo ") solution of benzo[*a*]quinolizinium salt (Xa) was evaporated *in vacuo*. A solution of the residual syrup in water (50 ml.) was shaken with activated charcoal to remove traces of sulphur, and the filtered liquid was divided into two equal portions (solutions " A " and " B "). Solution " A " was diluted with water to 50 ml. and treated slowly with 60% perchloric acid to pH *ca.* 2, and the resulting crystals (1·7 g.), m. p. 148—150°, were recrystallised from methanol, yielding colourless plates (1·43 g.), m. p. 150—152·5°, of cis-2-*methoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium* (Xa) *perchlorate*. A sample, recrystallised further, had m. p. 151—153° (Found: C, 53·9; H, 6·05; N, 3·45; Cl, 8·2. $C_{20}H_{28}ClNO_8$ requires C, 53·85; H, 6·3; N, 3·15; Cl, 7·95%), $\nu_{max.}$ 1738 (C=O) and 1649 cm.$^{-1}$ (C=N$^+$), $\lambda_{max.}$ (in EtOH) 246—247, 305, and 356—357 mμ (ε 16,500, 9370, and 10,100). Solution " B " was evaporated and a solution of the residue in methanol was brought to pH *ca.* 2 with methanolic hydrogen chloride and evaporated. The residual syrupy benzo[*a*]quinolizinium (Xa) chloride was dissolved in methanol (30 ml.) and shaken with platinum oxide (0·3 g.) under hydrogen, absorbing 167 ml. (19°/772 mm.) during 20 min. The filtered solution was concentrated to 30 ml. and treated with 60% perchloric acid (1 ml.), giving crystals (1·7 g.), m. p. 207—208·5°, of the perchlorate of the ester (IXa). Crystallisation of the derived base from petroleum (b. p. 60—80°) gave the original ester (IXa), m. p. 77·5—79°.

The non-crystalline ester (VIa) was converted by mercuric acetate in the above manner into the same benzo[*a*]quinolizinium salt (Xa) which, on hydrogenation, gave the ester (IXa), m. p. 78—79·5°.

(*b*) *The* 3,4-*dimethoxyphenethylamides* (IXb) *and* (VIb). A solution of the 3,4-dimethoxyphenethylamide (IXb) (0·5 g.) in 10% aqueous acetic acid (10 ml.) was refluxed with mercuric acetate (1·35 g.) for 50 min. The mixture was heated with water (35 ml.) and N-hydrochloric acid (5 ml.) on the steam-bath, saturated with hydrogen sulphide, cooled, filtered, and evaporated. A solution of the residual benzo[*a*]quinolizinium salt (Xb) in water (50 ml.) was shaken with activated charcoal, filtered, and treated with an excess of concentrated aqueous ammonia. The corresponding anhydro-base crystallised slowly, and after 16 hr. the crystals (0·45 g.), m. p. 157—158°, were collected. A solution in hot alcohol (25 ml.) was filtered from sediment and concentrated to *ca.* 15 ml., giving colourless needles (0·38 g.) of the *anhydro-base*, m. p. 157—158° depressed by starting material (Found: C, 70·35; H, 7·5; N, 5·35. $C_{29}H_{38}N_2O_5$ requires C, 70·4; H, 7·75; N, 5·65%), $\lambda_{max.}$ (in 0·1N-HCl–EtOH) 238 (infl.), 243, 287 (infl.), 305, and 352 mμ (ε 17,600, 17,900, 7360, 9630, and 10,300). Oxidation of the 3,4-dimethoxyphenethylamide (VIb) (0·4 g.) with mercuric acetate similarly gave 0·32 g. of an identical (mixed m. p., infrared and ultraviolet spectra) anhydro-base. Quantities of anhydro-base obtained from each of the 3,4-dimethoxyphenethylamides (IXb) and (VIb) were separately hydrogenated in methanolic hydrogen chloride in the presence of platinum. The resulting hydrochloride from each filtered solution was dissolved in water and basified with concentrated aqueous ammonia, giving an immediate precipitate of solid. Crystallisation of the solid from ethyl acetate gave, in each case, the 3,4-dimethoxyphenethylamide (IXb) (70%), m. p. 158—159°.

(+)-3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine*.—The seeds referred to below were obtained by addition of ether to an acetone solution of equimolecular quantities of the racemic 2-oxobenzo[*a*]quinolizine (I) and (+)-camphor-10-sulphonic acid, and recrystallisation of the resulting salt from acetone. Optical rotations of the (+)-camphor-10-sulphonates were determined in water (*c* 2), and those of the benzo[*a*]quinolizine bases in ethanol (*c* 1).

(*a*) A solution of the racemic 2-oxobenzo[*a*]quinolizine (1 g.) and (+)-camphor-10-sulphonic acid (0·88 g.) in hot ethyl acetate (50 ml.) was seeded and set aside at room temperature overnight. The resulting crystals of (+)-camphor-10-sulphonate (0·6 g.), $[\alpha]_D^{24}$ +28·5°, were dissolved in cold water and treated gradually with an excess of concentrated aqueous ammonia, giving crystals (0·29 g.), m. p. 116—117°, $[\alpha]_D^{25}$ +59°, of partly resolved base. Treatment of this base with (+)-camphor-10-sulphonic acid (0·28 g.) and ethyl acetate (20 ml.) as before gave a salt (0·34 g.), $[\alpha]_D^{25}$ +37°, the derived optically purer base (0·15 g.) having m. p. 118—119°, $[\alpha]_D^{24}$ +88·5°.

(*b*) A solution of the racemic 2-oxobenzo[*a*]quinolizine (10 g.) and (+)-camphor-10-sulphonic acid (8·1 g.) in hot ethyl acetate (150 ml.) was seeded and refluxed for 5 hr., and the resulting suspension of crystals was set aside at room temperature overnight. The salt (8·82 g.), $[\alpha]_D^{23}$ +38·5°, gave a base (4·5 g.), m. p. 112—117°, $[\alpha]_D^{23}$ +86·5°. The ethyl acetate liquors were evaporated and a solution of the residue in water (150 ml.) was decolorised with charcoal and basified with ammonia, giving a lævorotatory base (4·56 g.), m. p. 107—111°, $[\alpha]_D^{23}$ −30°.

(*c*) The same quantities of reagents as were used in (*b*) were refluxed for 11 hr. and, after only 2 hr. at room temperature, the resulting salt (11 g.), $[\alpha]_D^{24}$ +41°, was collected. It gave a base (5·53 g.), m. p. 113—117°, $[\alpha]_D^{24}$ +94·5°. The ethyl acetate liquors were concentrated to 50 ml. and refluxed for 12½ hr., the resulting salt (2·52 g.), $[\alpha]_D^{23}$ +41·5°, affording more base (1·12 g.), m. p. 112—117°, $[\alpha]_D^{23}$ +93·5°.

(*d*) A solution of the racemic 2-oxobenzo[*a*]quinolizine (100 g.) and (+)-camphor-10-sulphonic acid (85 g.) in hot ethyl acetate (1250 ml.) was seeded and refluxed, with stirring, for 28 hr. The resulting suspension of crystals was set aside at room temperature for 16 hr., then filtered, giving (+)-*base* (+)-*camphor*-10-*sulphonate* (145·6 g., 81%), m. p. 189—190° (effervescence), $[\alpha]_D^{26}$ +41° (Found: N, 2·6; S, 6·3. $C_{27}H_{39}NO_7S$ requires N, 2·7; S, 6·15%). A solution of this salt in cold water (3 l.) was treated gradually with an excess of concentrated aqueous ammonia, with seeding, and the resulting suspension of colourless prisms was set aside at 0° overnight and filtered, giving optically pure (+)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (76·7 g.), m. p. 116—120°, $[\alpha]_D^{24}$ +98°. Recrystallisation from petroleum (b. p. 60—80°) gave prisms, m. p. 121·5—123°, of the same optical rotation (Found: C, 70·7; H, 7·8; N, 5·05. $C_{17}H_{23}NO_3$ requires C, 70·55; H, 8·0; N, 4·85%). From the aqueous liquors a further 1·4 g. of base, m. p. 111—115°, $[\alpha]_D^{23}$ +77°, was also obtained. The ethyl acetate liquors gave 16·9 g. of optically inactive 2-oxobenzo[*a*]quinolizine.

To determine its optical stability under acid conditions, the (+)-base (0·25 g.) was heated with glacial acetic acid (0·015 ml.) in dry benzene (1·3 ml.) under reflux for 1½ hr. and the cooled solution was treated with water (10 ml.). After removal of the benzene *in vacuo*, the residual aqueous suspension of crystals was basified with ammonia and filtered, the crystals (0·21 g.) of base having $[\alpha]_D^{23}$ +74°. When the glacial acetic acid was increased to 0·1 ml., the derived base (0·2 g.) had $[\alpha]_D^{22}$ +18°. Heating the (+)-base (0·25 g.) in aqueous hydrochloric acid (5 ml.) at pH 5 for 75 min. at 95°, followed by addition of ammonia, gave a base (0·21 g.) of $[\alpha]_D^{22}$ +27°.

The (+)-base was converted, in the manner described above for the racemic compounds, through the (−)-unsaturated *ester* [mirror image of (III)], m. p. 105·5—107°, $[\alpha]_D^{23}$ −42° (*c* 1 in MeOH) (Found: C, 69·8; H, 8·0; N, 4·05. $C_{20}H_{27}NO_4$ requires C, 69·55; H, 7·9; N, 4·05%), into the (+)-saturated *ester* [mirror image of (Va)], double m. p. 98—99° and 101·5—102·5°, $[\alpha]_D^{23}$ +37° (*c* 1 in MeOH) (Found: C, 69·45; H, 8·3; N, 4·2. $C_{20}H_{29}NO_4$ requires C, 69·15; H, 8·4; N, 4·05%).

(−)-3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I).—Crystals of the (−)-camphor-10-sulphonate of the (−)-base were obtained by heating the base, $[\alpha]_D^{23}$ −30°, obtained as in (*b*) above, in ethyl acetate with (−)-camphor-10-sulphonic acid.[20] By using seeds of this salt, and the procedure described in (*d*) above, the racemic 2-oxobenzo[*a*]quinolizine (10 g.) was converted into the (−)-*base* (−)-*camphor*-10-*sulphonate* (15·6 g., 86%), $[\alpha]_D^{24}$ −43° (*c* 2 in H_2O) (Found: N, 2·5; S, 6·15. $C_{27}H_{39}NO_7S$ requires N, 2·7; S, 6·15%). This gave (−)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I) (7·8 g.), m. p. 116—120°, $[\alpha]_D^{23}$ −99° (*c* 1 in EtOH) (Found: C, 70·85; H, 7·85; N, 4·75. $C_{17}H_{23}NO_3$ requires C, 70·55; H, 8·0; N, 4·85%). From the ethyl acetate liquors 1·2 g. of racemic 2-oxobenzo[*a*]quinolizine were recovered.

Conversion of (−)-3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I) *into* (+)-O-*Methylpsychotrine* (XIII).—By the methods described above for the racemic compounds, the (−)-2-oxobenzo[*a*]quinolizine (I) was converted through the (+)-unsaturated *methyl ester* (III), m. p. 105·5—107°, $[\alpha]_D^{23}$ +42° (*c* 1 in MeOH) (Found: C, 69·5; H, 7·7; N, 4·15%), into the (−)-saturated methyl ester (Va), double m. p. 97—98° and 102—103°, $[\alpha]_D^{22}$ −36° (*c* 1 in MeOH) (Found: C, 69·05; H, 8·4; N, 4·0%). Battersby and Harper [12] give m. p. 98—99°, $[\alpha]_D^{20}$ −35·4° (*c* 2·82 in MeOH). The derived 3,4-dimethoxyphenethylamide (Vb) had m. p. 171·5—173° (lit.,[12] 171·5—172·5°) (Found: C, 70·25; H, 7·9; N, 5·6. Calc. for $C_{29}H_{40}N_2O_5$: C, 70·15; H, 8·1; N, 5·65%).

The corresponding ethyl ester was prepared by reaction of the (−)-2-oxobenzo[*a*]quinolizine (I) (10 g.) with ethoxycarbonylmethylenetriphenylphosphorane (27·1 g.), in the absence of solvent, at 152° for 2½ hr., the excess of phosphorane being decomposed with benzaldehyde in the usual manner. Crystallisation of the product from petroleum (b. p. 60—80°) and then from ethanol gave the (+)-unsaturated *ethyl ester* (III; CO_2Et for CO_2Me) (8·35 g., 67%), m. p. 117—119°, $[\alpha]_D^{21}$ +44° (*c* 1 in EtOH) (Found: C, 70·0; H, 8·1; N, 3·75. $C_{21}H_{29}NO_4$ requires C, 70·15; H, 8·15; N, 3·9%). Catalytic hydrogenation of this in ethanolic hydrogen chloride, in the presence of platinum, gave the (−)-saturated ethyl ester (V; R = EtO) (68%), m. p. 89—90° (lit.,[12] 88—90°), $[\alpha]_D^{23}$ −39° (*c* 1 in EtOH) (Found: C, 70·15; H, 8·45; N, 3·65. Calc. for $C_{21}H_{31}NO_4$: C, 69·75; H, 8·65; N, 3·9%). This ester was hydrolysed with 2N-hydrochloric acid and the derived carboxylic acid hydrochloride was dried and treated with thionyl chloride at room temperature. Reaction of the resulting acid chloride hydrochloride with 3,4-dimethoxyphenethylamine in the presence of an excess of triethylamine and recrystallisation of the product from ethyl acetate gave the 3,4-dimethoxyphenethylamide (Vb) (84%), m. p. 171·5—173°.

Cyclisation of the 3,4-dimethoxyphenethylamide (Vb), as described for the racemic compound, and treatment of the derived base with oxalic acid dihydrate in alcohol gave hydrated (+)-*O*-methylpsychotrine di(hydrogen oxalate) (80%), m. p. 162—163° (effervescence). The anhydrous salt had $[\alpha]_D^{22}$ +45·7° (*c* 2 in H_2O) (lit.,[21] +45·9°) (Found: C, 59·85; H, 6·3; N, 4·3. Calc. for $C_{33}H_{42}N_2O_{12}$: C, 60·2; H, 6·45; N, 4·25%). The (+)-*O*-methylpsychotrine base (XIII) obtained from the di(hydrogen oxalate) had m. p. 122·5—124·5° [lit.,[22] 123—124° (corr.)] (Found: C, 72·9; H, 7·95; N, 5·9. Calc. for $C_{29}H_{38}N_2O_4$: C, 72·75; H, 8·0; N, 5·85%), and was identical (mixed m. p., infrared spectrum) with the natural alkaloid.

[20] Burgess and Gibson, *J. Soc. Chem. Ind.*, 1925, 496T.
[21] Pyman, *J.*, 1917, **111**, 419.
[22] Brindley and Pyman, *J.*, 1927, 1067.

Emetine (XIV) *and Isoemetine* (XV).—(+)-*O*-Methylpsychotrine was reduced by a variety of procedures, as described below, and the relative proportion of emetine to isoemetine in each product of reduction was determined chromatographically in the following manner. A solution of the mixture of bases in trichloroethylene was poured through a column of activated alumina, and the eluting liquid was changed gradually from trichloroethylene to methylene chloride. The fractions were separately treated with a slight excess of aqueous hydrogen bromide, and the organic solvent was evaporated *in vacuo*, the residual aqueous solutions giving in each case emetine dihydrobromide, needles, m. p. 250—254° (Found, on dried material: C, 54·15; H, 6·65; N, 4·25; Br, 25·0. Calc. for $C_{29}H_{42}Br_2N_2O_4$: C, 54·2; H, 6·6; N, 4·35; Br, 24·9%). Further elution of the column with chloroform, and similar treatment of the chloroform solutions, yielded isoemetine dihydrobromide, prisms which formed a glass at 215—220° (Found, on dried material: C, 54·05; H, 6·45; N, 4·3; Br, 24·65%) and gave hydrated isoemetine base, m. p. 95—96° (lit.,[23] 97—98°).

Reduction of (+)-*O*-methylpsychotrine with lithium aluminium hydride in ether, or with potassium borohydride in methanol, gave approximately equal amounts of emetine and isoemetine. Hydrogenation in methanolic triethylamine with Raney nickel, or in methanolic potassium hydroxide with platinum, gave an emetine : isoemetine ratio of 1·4 : 1. The best yield of emetine was obtained with platinum in methanolic sodium methoxide, the ratio being 1·8 : 1. Hydrogenation in aqueous solution at pH *ca.* 5 gave some emetine (cf. Karrer, Eugster, and Rüttner [13]), but isoemetine was the main product by a factor of 3·5 : 1.

For the isolation of emetine from the product of hydrogenation of (+)-*O*-methylpsychotrine (with platinum in methanolic sodium methoxide) it sufficed to treat a methanolic solution of the resulting bases with a slight excess of concentrated aqueous hydrogen bromide. Emetine dihydrobromide (47%) crystallised, the isoemetine dihydrobromide and some emetine dihydrobromide remaining in the liquors.

The emetine dihydrobromide obtained was identical with the natural material in infrared absorption and in biological activity.

Reconversion of Isoemetine into (+)-O-*Methylpsychotrine.*—(*a*) A mixture of isoemetine hydrate (1 g.), nitrobenzene (0·5 g.), mesitylene (2 ml.), and 10% palladised charcoal (0·25 g.) was heated in a bath at 180° for 1½ hr., the hydrogen liberated being entrained in a current of carbon dioxide. The reaction product was digested with hot alcohol (50 ml.), the filtered solution was evaporated, and the residue was treated with oxalic acid dihydrate (1 g.) in alcohol (30 ml.), giving somewhat impure hydrated (+)-*O*-methylpsychotrine di(hydrogen oxalate) (0·57 g.), m. p. 157—160° (effervescence), $[\alpha]_D^{25}$ +36° (*c* 2 in H_2O).

(*b*) Aqueous sodium hypochlorite (2·06M; 0·49 ml.) was added dropwise to a solution of isoemetine hydrate (0·5 g.) in methanol (4 ml.). After 15 min., the solution, containing suspended sodium chloride, was treated with a solution prepared from sodium (0·31 g.) in methanol (8 ml.) and refluxed for 45 min. The cooled mixture was diluted with water, the methanol was evaporated *in vacuo*, and the residual aqueous suspension of gum was extracted with trichloroethylene. The base recovered from the trichloroethylene was heated with oxalic acid dihydrate in alcohol (20 ml.) and set aside, giving hydrated (+)-*O*-methylpsychotrine di(hydrogen oxalate) (0·66 g., 91%), m. p. 161—162° (effervescence), $[\alpha]_D^{25}$ +41° (*c* 2 in H_2O).

N-Chlorosuccinimide was equally effective for the above conversion, whilst the use of chloramine-T, dichloramine-T, or sodium hypobromite led to 60—70% yields of (+)-*O*-methylpsychotrine.

3,4-Dihydro-6,7-dimethoxyisoquinoline from the Tetrahydro-derivative.—A stirred solution of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (from 477 g. of the hydrochloride) in methanol (2500 ml.) at 0° was treated with 1·83M-aqueous sodium hypochlorite (1140 ml.) during 15 min., with cooling at *ca.* −5°. An exothermic reaction occurred, the temperature rising to 34°, and sodium chloride separated. After 1 hr. at room temperature sodium hydroxide (770 g.) was added, the stirred mixture was refluxed for 45 min. and diluted with water (3000 ml.), and the methanol was evaporated *in vacuo*. The residual aqueous suspension was extracted with chloroform and the base, recovered from the chloroform solution, was freed from traces of chloroform by distillation with ether. A solution of the base in ether (1150 ml.) was treated cautiously with powdered carbon dioxide, filtered from precipitated solid (8 g.), and evaporated. The residual 3,4-dihydro-6,7-dimethoxyisoquinoline (387 g., 97%), b. p. *ca.* 120°/0·01 mm.,

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

slowly crystallised as needles (Found: C, 68·75; H, 6·9; N, 7·2. Calc. for $C_{11}H_{13}NO_2$: C, 69·1; H, 6·85; N, 7·35%), $\lambda_{max.}$ (in 0·01N-NaOH–EtOH) 231, 280, and 310 mμ (ε 25,200, 6950, and 6070).

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