499. *The Synthesis of Emetine and Related Compounds. Part II.* The Synthesis of (±)-Rubremetinium Bromide.*

By Alan R. Battersby, H. T. Openshaw, and Hamish C. S. Wood.

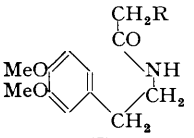
The hexahydro-oxoquinolizine derivative (V) has been synthesised from (I; R = CO_2Et or CN) and converted by two methods into (±)-rubremetinium bromide. The structural identity of the product with (+)-rubremetinium bromide derived from emetine has been shown spectroscopically, thus confirming the structure of the alkaloid.

In Part I * we gave a preliminary account of the confirmation of the structure of emetine by the total synthesis of (±)-rubremetinium bromide. We now describe this synthesis in full, together with an improved method.

3 : 4-Dimethoxyphenethylamine reacts with ethoxycarbonylacetyl chloride, or more conveniently with excess of ethyl malonate at 125°, to give ethyl *N*-3 : 4-dimethoxyphenethylmalonamate (I; R = CO_2Et), which is cyclised by phosphoric oxide to ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate (II; R = CO_2Et), but this compound is prepared most satisfactorily by Osbond's method (*J.*, 1951, 3464). It is hydrogenated smoothly to the tetrahydro*iso*quinoline (III). Two methods were investigated for the conversion of (III) into (IV). In spite of unfavourable indications in the literature (see, for example, Philippi and Galter, *Monatsh.*, 1929, **51**, 253) piperidine was found to add smoothly to ethyl α-ethylacrylate, yielding ethyl 1-piperidinobutane-2-carboxylate, but the reaction of (III) with the acrylate was complex and did not lead to the desired product. Condensation of (III) with ethyl α-formylbutyrate, followed by hydrogenation (cf. Décombe, *Ann. Chim.*, 1932, **18**, 81), effected partial conversion into (IV), and repetition of the process gave an acceptable yield. Dieckmann cyclisation followed by acid hydrolysis led to the oxoquinolizine derivative (V) in good yield. The ketone (V) contains two asymmetric centres, but since one of these is adjacent to the carbonyl group and may readily suffer inversion through enolisation, the single crystalline isomer isolated is probably the more stable form. The slow deposition of further crops of pure crystalline ketone from the mother-liquors may be due to inversion of small amounts of the less stable isomer contained in them.

* A paper by Battersby and Openshaw in *Experientia*, 1950, **6**, 387, is considered as Part I.

McElvain and Lyle (*J. Amer. Chem. Soc.*, 1950, **72**, 384) have shown that 1-methyl-4-piperidone condenses with ethyl cyanoacetate, and we have successfully converted the condensation product by hydrolysis, hydrogenation, and esterification into ethyl 1-methyl-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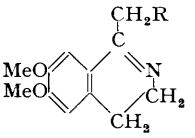
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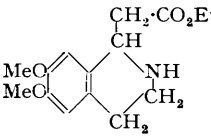
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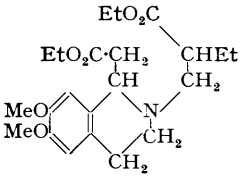
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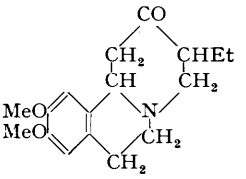
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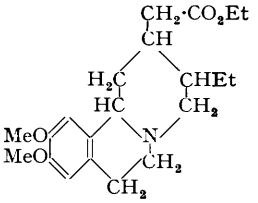
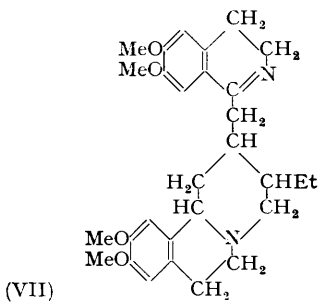

(VI)

4-piperidylacetate. By applying a similar procedure to the ketone (V), the ester (VI) was obtained, although not in an analytically pure condition. It was heated with 3 : 4-dimethoxyphenethylamine, and the product was cyclised with phosphoryl chloride. The resulting mixture of bases yielded no crystalline derivatives, but it was shown to contain the expected product (VII), structurally identical with *O*-methylpsychotrine, since oxidation with mercuric acetate gave a small amount of (±)-rubremetinium bromide (VIII). This product had an ultra-violet and visible absorption spectrum identical with that of (+)-rubremetinium bromide obtained by similar oxidation of emetine (Part I, *loc. cit.*).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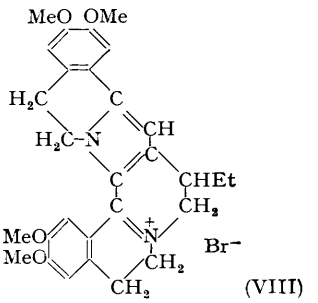
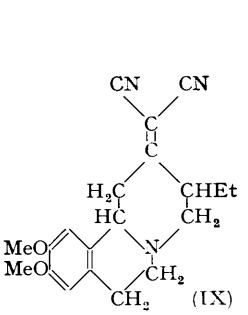

(VIII)

The very poor yield obtained in the above synthesis, and the failure to obtain pure crystalline products beyond the stage of the ketone (V), led us to seek improvements in the later stages, particularly as our ultimate aim is the synthesis of a product having the correct stereochemical configuration as well as the structure of emetine.

The ketone (V) was found to condense with malononitrile to give a crystalline product (IX) in excellent yield, but attempts to hydrogenate and to hydrolyse this substance gave unsatisfactory results. 1-Cyanomethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (II; R = CN) possesses a methylene group situated very similarly to that of malononitrile, but a series of model experiments (Morgan and Openshaw, forthcoming paper) showed that it cannot be condensed with ketones. Its precursor, α-cyano-*N*-3 : 4-dimethoxyphenethylacetamide (I; R = CN), however, condenses smoothly with ketones, and the products, after hydrogenation, can be cyclised to dihydro*iso*quinolines. When this process was applied to the ketone (V), a crystalline condensation product (X) was obtained in satisfactory yield. Attempted cyclisation of this product with phosphoric oxide led to its breakdown, the only product isolable after hydrolysis being 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline. Hydrogenation of (X) gave a crystalline dihydro-compound (XI), cyclisation of which was effected by phosphoric oxide in boiling *pseudo*cumene (lower

temperatures were ineffective), and after hydrolysis and decarboxylation the crude base (VII) was obtained in about 33% yield. On oxidation with mercuric acetate a 25% yield of (±)-rubremetinium chloride was obtained. Comparison with the maximum yield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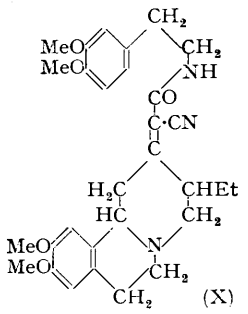
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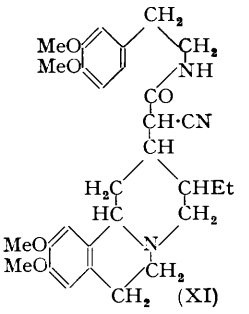
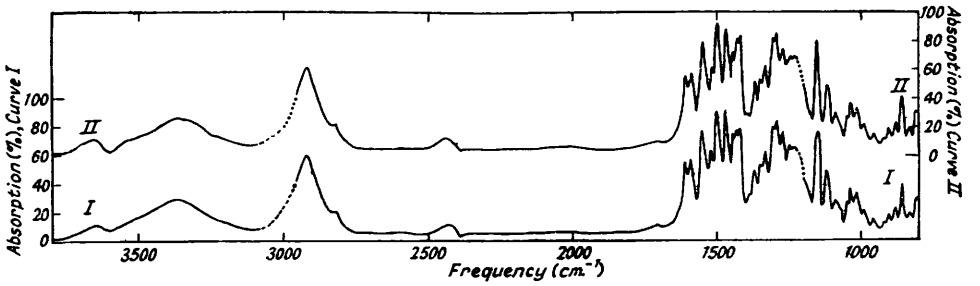

(XI)

(45%) obtained in the oxidation of emetine (Battersby and Openshaw, *J.*, 1949, S 67) suggests that the crude base contained over 50% of the expected product (VII). The (±)-rubremetinium chloride, after further purification, was converted into the bromide, which was shown to be structurally identical with (+)-rubremetinium bromide by a comparison of the infra-red absorption spectra (see Figure) of their chloroform solutions.



Infra-red absorption in chloroform. I, "Natural" (+)-rubremetinium bromide. II, Synthetic (±)-rubremetinium bromide. (Broken lines indicate zones of strong solvent absorption.)

While the work described in this paper was in progress, Preobrashenski and his co-workers (*Doklady Akad. Nauk*, S.S.S.R., 1950, **75**, 539; 1951, **81**, 421) gave a preliminary account of a complete synthesis of emetine, but full details, particularly of the separation of the various stereoisomers which would be expected, do not appear to have been published yet. Pailer and Strohmayer (*Monatsh.*, 1951, **82**, 1125) and Pailer, Schneglberger, and Reifschneider (*Monatsh.*, 1952, **83**, 513) have described the synthesis by two methods of racemic *C*-noremetine, which lacks the *C*-ethyl group of emetine.

Experimental

Ethyl N-3 : 4-*Dimethoxyphenethylmalonamate* (I; R = CO_2Et).—(*a*) A stirred solution of 3 : 4-dimethoxyphenethylamine (46·5 g.) in anhydrous ether (250 ml.) was treated dropwise with a solution of ethoxycarbonylacetyl chloride (19·5 g., 0·5 equiv.) in anhydrous ether (50 ml.). After 12 hr., water (100 ml.) was added, the aqueous layer was separated, and the ethereal layer was extracted with hydrochloric acid (10 ml. of 2N). The combined aqueous layers were saturated with ammonium sulphate and extracted successively with ether (4 × 200 ml.) and ethyl acetate (3 × 200 ml.); evaporation of the combined extracts yielded *ethyl* N-3 : 4-*dimethoxyphenethylmalonamate* (35·9 g., 93·5%), which after distillation at 110° (bath)/10^{-5} mm. crystallised from anhydrous ether as colourless needles, m. p. 63—64° (Found: C, 60·6; H, 7·25; N, 5·05. $C_{15}H_{21}O_5N$ requires C, 60·9; H, 7·2; N, 4·75%).

(*b*) (With Arthur Morgan.) 3 : 4-Dimethoxyphenethylamine (4·23 g.) was heated with ethyl malonate (11·2 g.) for 4½ hr. at 125°. Excess of ethyl malonate was removed by distillation at 10 mm., and the residue was distilled in a high vacuum. A colourless oil distilled at

175—190°/2 × 10^{-4} mm. and solidified on cooling. Crystallisation from ether gave colourless needles, m. p. 52—53° (4·83 g., 70%), sufficiently pure for cyclisation to the dihydro*iso*quinoline.

Ethyl 3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylacetate* (II; R = CO_2Et).—A boiling solution of the foregoing compound (15·75 g.) in pure anhydrous toluene (300 ml.) was treated with phosphoric oxide (30 g.). The mixture was agitated, and the solid material occasionally broken up by means of a spatula. Further portions (2 × 30 g.) of phosphoric oxide were added after 10 and 25 min., and heating under reflux was continued for a total of 45 min. The mixture was well cooled whilst water (500 ml.) was added in portions. The aqueous layer was separated and the toluene layer extracted twice with hydrochloric acid (2 × 30 ml. of 2N). The combined aqueous solutions were washed twice with ether, made alkaline with a large excess of concentrated aqueous potassium carbonate, and extracted with ether (5 × 200 ml.). Evaporation of the dried extract left the crude *dihydro*iso*quinoline* as a clear reddish-brown gum (11·12 g., 75%), which crystallised from ether or acetone–light petroleum as pale yellow rhombic plates (9·8 g.), m. p. 84—85° raised to 85·5—86·5° by distillation at 130° (bath)/0·4 mm. and crystallisation from ether. For analysis it was dried at 56° for 1½ hr. over phosphoric oxide in a vacuum (Found: C, 64·9; H, 7·05; N, 5·20. $C_{15}H_{19}O_4N$ requires C, 64·95; H, 6·95; N, 5·05%). The *picrate* separated from ethanol as bright yellow rods, m. p. 165—167° (decomp.), raised by repeated crystallisation from ethyl acetate and ethanol to 168—169·5° (decomp.); it was dried at 100° for 1½ hr. over phosphoric oxide in a vacuum (Found: C, 50·0; H, 4·3; N, 10·9. $C_{21}H_{22}O_{11}N_4$ requires C, 49·8; H, 4·4; N, 11·0%). When crystallised from ethyl acetate, the picrate melted consistently at 161—163° (decomp.) and was converted into the higher-melting form on crystallisation from ethanol.

Cyclisation of the malonamate by means of phosphoryl chloride in boiling toluene was much less satisfactory than the above method.

Ethyl 1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylacetate* (III).—A solution of the dihydro*iso*quinoline (21·54 g.) in acetic acid (200 ml.) was shaken with hydrogen and platinic oxide (0·2 g.); absorption of hydrogen (1·0 mol.) ceased after 2 hr. The filtered solution was evaporated to dryness and the residual gum was dissolved in water, half saturated with ammonium sulphate, made just alkaline to phenolphthalein with potassium carbonate, and extracted with ethyl acetate (5 × 150 ml.). The dried extract was evaporated and the residual yellow gum (20·28 g.) was distilled at 160° (bath)/5 × 10^{-3} mm. The distillate, which crystallised, was recrystallised twice from ether to give pale yellow rhombs (16·7 g., 77%), m. p. 75·5—76·5°. Recrystallisation thrice more from ether gave the pure *base* as colourless prisms, m. p. 77—78°, which were dried at 56° for 1½ hr. over phosphoric oxide in a vacuum (Found: C, 64·6; H, 7·5; N, 5·3. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·6; N, 5·0%). The *picrate* crystallised from ethanol as golden-yellow needles, m. p. 181—183° (Found: C, 49·8; H, 4·8. $C_{21}H_{24}O_{11}N_4$ requires C, 49·6; H, 4·8%).

Ethyl 1-*Piperidinobutane*-2-*carboxylate*.—(*a*) A mixture of ethyl α-ethylacrylate (3·2 g.) (Mannich and Ritsert, *Ber.*, 1925, **57**, 1117) and piperidine (2·1 g.) was kept at room temperature for 10 days. On distillation a small low-boiling fraction was removed, and the main fraction (3·28 g.) boiled at 107—109°/7 mm. It was dissolved in dilute hydrochloric acid, and the solution was extracted with ether. The product was reprecipitated by the addition of ammonia, extracted with ether and redistilled at 109—110°/8 mm., giving *ethyl* 1-*piperidinobutane*-2-*carboxylate* as a colourless oil (2·88 g.) from which no crystalline derivatives could be obtained (Found: C, 67·5; H, 10·6; N, 6·2. $C_{12}H_{23}O_2N$ requires C, 67·5; H, 10·9; N, 6·6%).

(*b*) Piperidine (0·7 g.) and ethyl α-formylbutyrate (1·2 g., 1 equiv.) (cf. Décombe, *loc. cit.*; Ingold, Perren, and Thorpe, *J.*, 1922, **121**, 1782) were mixed, considerable heat being developed. After 1 hr. the oil was taken up in ether, dried (Na_2SO_4) and distilled; ethyl 1-piperidinobut-1-ene-2-carboxylate (1·3 g., 75%) was collected as a pale yellow oil, b. p. 135°/4 mm. Its solution in ethanol (30 ml.) was shaken with hydrogen and platinic oxide (0·1 g.), absorption of hydrogen (1·1 mol.) ceasing after 4 hr. After removal of the catalyst and evaporation of the solvent, the product distilled at 108—110°/9 mm. as a colourless oil (1·2 g.).

2-(2-*Ethoxycarbonylbutyl*)-1-*ethoxycarbonylmethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*iso*quinoline* (IV).—A solution of the tetrahydro*iso*quinoline (III) (3·94 g.) in anhydrous benzene (40 ml.) was heated with ethyl α-formylbutyrate (2·5 g., 1·2 equiv.) under a 15-cm. Vigreux column, so that slow distillation of benzene occurred; the volume was kept constant by the addition of dry benzene to the mixture. After 1¼ hr., when about 100 ml. of benzene had distilled, the mixture was evaporated on the steam-bath in a vacuum, and the residue was dissolved in acetic acid (30 ml.) and shaken with hydrogen and platinic oxide (0·2 g.); 1·02 mol. of hydrogen were absorbed in 1¾ hr. (Both the product and the unchanged ethyl α-formyl-

butyrate are reduced by this process.) After filtration, the solvent was evaporated under reduced pressure and the residue was taken up in N-hydrochloric acid (40 ml.) and washed with ether (3 × 50 ml.). The aqueous solution was treated with a large excess of solid potassium carbonate, and the product was extracted with ether (3 × 100 ml.). The extract, after being washed with water (10 ml.), dried, and evaporated yielded a yellow gum (4·56 g.). This was treated with ethyl α-formylbutyrate (2·0 g.) as before, and the crude product was hydrogenated in acetic acid solution, 0·41 mol. of hydrogen being absorbed. The basic material (5·3 g.) was isolated from the product as before, and was freed from unchanged secondary base by heating it with acetic anhydride (15 ml.) on the steam-bath for 1½ hr., basic material being then isolated in the usual way. The clear yellow gum (4·35 g., 75%) thus obtained was distilled twice at 120° (bath)/8 × 10^{-5} mm., giving an almost colourless gum (Found: C, 64·8; H, 8·4; N, 3·3. $C_{22}H_{33}O_6N$ requires C, 64·7; H, 8·15; N, 3·45%). The *diester* subsequently crystallised, and after recrystallisation thrice from light petroleum (b. p. 40—60°) formed colourless rods, m. p. 76—77°.

Heating together the tetrahydro*iso*quinoline (III) and ethyl α-ethylacrylate at 75—85° for 40 hr. failed to give the desired substance (IV). The product, after removal of neutral material and secondary base as above, distilled at 120° (bath)/2 × 10^{-5} mm. as a yellow gum (Found: C, 65·0; H, 7·55; N, 4·8%).

3-*Ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxy*-2-*oxobenzo*[a]*quinolizine* (V).—The foregoing diester (10·4 g.) in anhydrous toluene (50 ml.) was added during 3 min. to a stirred suspension of freshly prepared sodium ethoxide (1·8 g.) in anhydrous toluene (60 ml.). The mixture was stirred and the alcohol formed in the reaction was removed by allowing slow distillation of a part of the toluene through a 7″ Vigreux column for 1 hr. After being boiled under reflux for a further hr., the solution was cooled in ice to precipitate the sodium salt of the product, the toluene was decanted, and the salt was hydrolysed by being heated with 2N-hydrochloric acid (150 ml.) for 7½ hr. at 100°. The cooled solution was washed twice with ether, basified with a large excess of solid potassium carbonate, and extracted with ether (5 × 75 ml.). Evaporation of the dried extract left a brownish solid (6·06 g., 82%), which crystallised from ether as pale yellow needles (5·12 g.), m. p. 108—109° after sintering at 107°; after recrystallisation from ether and sublimation at 120°/0·4 mm. the *ketone* (V) formed colourless needles, m. p. 109—109·5° (Found: C, 70·3; H, 7·8; N, 5·1. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 8·0; N, 4·9%). Evaporation of the ethereal mother-liquors from the crystallisation left a yellow gum which was twice distilled at 130° (bath)/5 × 10^{-4} mm. (Found: C, 69·3; H, 7·7; N, 4·9%). Gradual concentration of an ethereal solution of the distillate gave successive crops of the crystalline ketone.

Ethyl 1-*Methyl*-4-*piperidylacetate*.—Ethyl α-cyano-1-methyl-4-piperidylideneacetate (1·57 g.) (McElvain and Lyle, *J. Amer. Chem. Soc.*, 1950, **72**, 384) was hydrolysed by being heated under reflux with 2N-hydrochloric acid (20 ml.) for 8 hr. The solution was made alkaline to phenolphthalein and extracted thrice with ether, the aqueous solution being retained for further treatment (see below). The ethereal extract after drying and evaporation yielded an oil (0·675 g.), which distilled completely at 99—101°/6 mm. to give a colourless, unsaturated base, presumed to be 1-methyl-4-piperidylideneacetonitrile. A portion (0·37 g.) was dissolved in ethanol and shaken with hydrogen and palladised strontium carbonate (0·5 g.) until one mol. of hydrogen had been absorbed (1 hr.). Uptake of hydrogen continued beyond this point, but the hydrogenation was stopped, the catalyst was removed by filtration, and the solution was evaporated to dryness. The residue was dissolved in aqueous ethanol (8 ml. of 50%) containing potassium hydroxide (2 g.) and heated under reflux for 26 hr. The solution was acidified with hydrochloric acid and evaporated to dryness, and the residue was extracted thoroughly with absolute ethanol. The extract was evaporated to dryness, and the residue was again taken up in absolute ethanol (20 ml.) and filtered from traces of potassium chloride. The solution was mixed with concentrated sulphuric acid (0·5 ml.) and heated under reflux for 3 hr. After being concentrated to about 10 ml., the solution was poured into concentrated aqueous potassium carbonate, and the liberated amino-ester (0·39 g.) was isolated by ether-extraction. It distilled at 100° (bath)/15 mm. as a colourless oil, and yielded a *picrate*, m. p. 160—161°, as yellow needles from alcohol (Found: C, 46·2; H, 5·2; N, 13·8. $C_{16}H_{22}O_9N_4$ requires C, 46·4; H, 5·4; N, 13·5%).

The aqueous alkaline liquor from the original hydrolysis was acidified with hydrochloric acid and evaporated to dryness. The residue was extracted with glacial acetic acid (20 ml.), and the filtered extract, containing the acidic products of the hydrolysis, was boiled under reflux for 9 hr. The solvent was evaporated, and the residue was dissolved in water, made alkaline with potassium hydroxide, and extracted 4 times with ether, which removed only a trace of a

yellow oil. The aqueous solution was again acidified, evaporated to dryness, and extracted with glacial acetic acid, the extract on evaporation leaving crude 1-methyl-4-piperidylideneacetic acid as a brown gum (0·47 g.). It was dissolved in aqueous acetic acid and shaken with hydrogen and platinic oxide (0·05 g.), 1·0 mol. of hydrogen being absorbed in 1½ hr. The product was esterified as described above, yielding a yellow oil (0·4 g.) which distilled at 100° (bath)/15 mm. and gave a picrate, m. p. 157—159°, identical with that obtained previously.

Ethyl 3-*Ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizin*-2-*ylacetate* (VI).—A mixture of the 2-oxoquinolizine (V) (1·74 g.), ethyl cyanoacetate (2 g.), glacial acetic acid (0·29 g.), ammonium acetate (0·105 g.), and benzene (1·5 ml.) was heated so that slow distillation of benzene occurred. Dry benzene was added to the mixture to keep the volume constant. After 2 hr. the benzene was evaporated, and the residue was dissolved in 3N-hydrochloric acid (50 ml.). The solution was extracted twice with ether to remove a red oil (0·336 g.) which was rejected, and it was then boiled under reflux for 24 hr., made alkaline with potassium carbonate, and extracted with ether (4 × 75 ml.). The extract on evaporation left a yellow gum (0·364 g.) which partly crystallised when seeded with the oxoquinolizine, and which also contained some unsaturated material; it was not examined further. The aqueous phase was acidified to Congo-red with hydrochloric acid and evaporated to dryness under reduced pressure, and the residue was extracted several times with glacial acetic acid (total, 125 ml.). The filtered extract was boiled under reflux for 14 hr. and evaporated under reduced pressure. The residue was dissolved in water, basified, and extracted with ether which removed a little yellow gum (25 mg.). The aqueous solution was acidified and evaporated, and the residue was extracted with absolute ethanol. The extract was freed from inorganic salts by evaporation and re-extraction with ethanol. Evaporation then left the amino-acid fraction as a pale yellow resin (1·82 g.), which was dissolved in glacial acetic acid (20 ml.) and hydrogenated over platinic oxide, absorption of hydrogen (58 ml., *ca.* 0·5 mol.) ceasing after ¾ hr. After removal of catalyst and solvent, the product was dissolved in ethanol (100 ml.) containing sulphuric acid (3 ml.). The solution was heated under reflux for 3 hr., concentrated to 20 ml., and poured into ether (300 ml.) and concentrated aqueous potassium carbonate (40 ml.). The ester was isolated from the ethereal layer as a dark red-brown gum (1·34 g.), which on distillation at 120° (bath)/2 × 10^{-5} mm. gave a yellow gum (0·911 g.), unaffected by being shaken in ethanol with hydrogen and platinic oxide. After two further distillations at 100—110° (bath)/4 × 10^{-5} mm. the ester was still not pure (Found: C, 63·9; H, 8·0; N, 3·9. Calc. for $C_{21}H_{31}O_4N$: C, 69·8; H, 8·7; N, 3·9%).

2-*Dicyanomethylene*-3-*ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizine* (IX).—The ketone (V) (1·8 g.), malononitrile (0·5 g.), ammonium acetate (0·2 g.), acetic acid (0·4 g.), and anhydrous benzene (5 ml.) were heated at 125° under a short column. Fresh benzene was added to replace that which distilled, and after 45 min. water no longer distilled with the benzene. Ether (50 ml.) was added to the cooled mixture, and dry hydrogen chloride was passed in; an amorphous, hygroscopic hydrochloride was precipitated. The solvent was decanted and the precipitate was dissolved in water and treated with alkali. The liberated yellow base crystallised on contact with ether, and had m. p. 153—154° (1·99 g., 95%). By crystallisation from ether (400 ml.) in a Soxhlet apparatus the condensation *product* formed fine yellow needles (1·7 g.), m. p. 157—158°, raised on further crystallisation to 159—159·5° (Found: C, 71·0; H, 6·8; N, 12·6. $C_{20}H_{23}O_2N_3$ requires C, 71·2; H, 6·9; N, 12·5%).

Condensation of the Ketone (V) *with* α-*Cyano*-N-3 : 4-*dimethoxyphenethylacetamide*.—The ketone (3·0 g.), α-cyano-*N*-3 : 4-dimethoxyphenethylacetamide (2·6 g.) (Child and Pyman, *J.*, 1931, 36), and dry ammonium acetate (1·0 g.) were heated in dry benzene (25 ml.) so that slow distillation of benzene occurred, the volume of the reaction mixture being kept constant by addition of fresh benzene at the same rate. After 4 hr. the benzene was distilled off and the residue dissolved in 2N-hydrochloric acid (30 ml.). The solution was thoroughly extracted with ether which removed α-cyano-*N*-dimethoxyphenethylacetamide (0·56 g.), then basified with a large excess of solid potassium carbonate, and again extracted with ether (7 × 70 ml.). The ethereal extract yielded a yellow gum (4·29 g.) which was dissolved in 9 : 1 benzene–light petroleum (200 ml.) and chromatographed on alumina. The chromatogram was developed with benzene containing a trace of ethanol, two clearly defined fractions passing through. The first (0·84 g.) gave on crystallisation from ether the unchanged ketone (0·6 g.), m. p. and mixed m. p. 107—108°. The second (2·14 g.) crystallised from ether to give crude 2-[α-*cyano*-α-(N-3 : 4-*dimethoxyphenethylcarbamyl*)*methylene*]-3-*ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizine* (X) (1·44 g.), m. p. 128—133°. Further elution of the column and further chromatography of the eluate gave an additional quantity (0·24 g.) of the desired product. Further purification of the product by crystallisation from ether in a Soxhlet apparatus gave

yellow needles, m. p. 147—147·5°, which were dried at 80° in a vacuum over phosphoric oxide (Found : C, 69·0; H, 7·0; N, 7·7. $C_{30}H_{37}O_5N_3$ requires C, 69·3; H, 7·2; N, 8·1%).

The product having been obtained crystalline by this procedure, it was possible to simplify subsequent preparations. Thus, the ketone (5 g.) yielded 6·76 g. of crude material from the ethereal extract, and this was dissolved in dry ether (100 ml.) and seeded with the pure product. The crystals (2·56 g.; m. p. 137—139°) which slowly separated were collected, and the mother-liquor was evaporated to dryness. The residue, mainly unchanged ketone, was again treated with cyanodimethoxyphenethylacetamide and by the same process yielded the crystalline product (2·71 g.; m. p. 133—135°). Recrystallisation of the combined products gave fairly pure material (4·8 g.; m. p. 141—143°) which was further purified as above.

Attempted Cyclisation of the Condensation Product (X).—A portion of the above product (0·1 g.) was cyclised with phosphoric oxide (2 g.) in toluene in the usual manner, and the basic product (88 mg.) was dissolved in benzene–light petroleum and passed through a column of alumina. A small first fraction was rejected, and the main eluate (51 mg.) was further chromatographed similarly and freed from solvent at 100° in a high vacuum for 3 hr. (Found : C, 70·3; H, 6·9; N, 8·1. Calc. for $C_{30}H_{35}O_4N_3$: C, 71·8; H, 7·0; N, 8·04%). The analytical results indicated that the product was contaminated with the original amide and, in an attempt to remove this by hydrolysis, the material (35 mg.) was heated under reflux for 5 hr. with constant-boiling hydrochloric acid. After cooling and removal of neutral products by ether-extraction, the basic material (20 mg.) was recovered as usual, and its solution in benzene–light petroleum (70 : 30) was passed through a column of alumina. Elution with benzene containing a little ethanol gave one main fraction (15 mg.) which partly crystallised; the crystals, m. p. 97·5—98·5°, were identified by mixed m. p. as 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline (m. p. 102—103°).

2-[α-*Cyano*-α-(N-3 : 4-*dimethoxyphenethylcarbamyl*)*methyl*]-3-*ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizine* (XI).—A solution of the foregoing product (X) (0·61 g.) in absolute ethanol (150 ml.) was hydrogenated at atmospheric temperature and pressure over palladised strontium carbonate (6 g.), absorption of hydrogen (1·0 mol.) ceasing after 3 hr. After filtration, evaporation, and treatment with ether, the *product* (0·61 g.) crystallised (m. p. 165—169°); recrystallisation from ether (Soxhlet) and from ethanol gave colourless needles, m. p. 174—175° (Found : C, 68·8; H, 7·7; N, 8·4. $C_{30}H_{39}O_5N_3$ requires C, 69·05; H, 7·56; N, 8·1%).

(±) *Rubremetinium Bromide*.—(*a*) The ester (VI) (0·485 g.) and 3 : 4-dimethoxyphenethylamine (0·27 g.) were mixed and heated at 190° for 2 hr. A further portion (0·1 g.) of the amine was added and heating continued at 210° for 5 hr. The product, a dark resin, was freed from excess of amine and unchanged ester in a short-path still at 130—140° (bath)/4 × 10^{-5} mm. during several hr., and was then distilled at 200° (bath)/4 × 10^{-5} mm.; it then formed a yellow resin which could not be crystallised. A portion of the distilled amide (0·212 g.) was heated with purified toluene (5 ml.) and phosphoryl chloride (1 ml.) under reflux for 75 min. After being cooled, the toluene solution was extracted with water (15 ml.) and with 2N-hydrochloric acid (2 × 5 ml.). The combined acid extracts were basified with potassium hydroxide and extracted thrice with ether (total, 300 ml.), yielding after drying and evaporation a brownish gum (0·124 g.). Distillation gave fractions (i) b. p. 140—150° (bath)/4 × 10^{-5} mm. (57 mg.) and (ii) b. p. 180° (bath)/4 × 10^{-5} mm. (48 mg.). Fraction (ii) was shown to contain the desired product by its oxidation with mercuric acetate (*J.*, 1949, S 67) to (±)-rubremetinium bromide. Cyclisation of the amide with phosphoric oxide gave a similar result.

(*b*) A solution of the dimethoxyphenethylamide (XI) (2·53 g.) in purified *pseudo*cumene (50 ml.) was boiled under reflux for 1·5 hr., phosphoric oxide (24 g.) being added in 3 portions during the first hour. Water (100 ml.) was added to the cooled mixture, the acid aqueous layer was separated, and the *pseudo*cumene was extracted twice with dilute hydrochloric acid. The combined aqueous extracts were washed with ether, basified with excess of potassium hydroxide, and extracted with ethyl acetate (5 × 100 ml.). Evaporation of the extracts yielded a red gum (2·02 g.) which was treated with ether (2 × 100 ml.) to separate it into soluble (1·13 g.) and insoluble (0·89 g.) fractions. A portion (0·12 g.) of the latter was crystallised from ethanol, to give impure starting material (81 mg.), m. p. 166—169° (mixed m. p. 169—172°). The ether-insoluble fraction was therefore treated again with phosphoric oxide (3 × 4 g.) in *pseudo*cumene and gave a further 0·37 g. of ether-soluble base (total, 1·5 g.; 61%). The product was hydrolysed and decarboxylated by being boiled under reflux with 6N-sulphuric acid (100 ml.) for 24 hr. The solution was then made alkaline with sodium hydroxide and extracted with ether (5 × 100 ml.), the extracts yielding a clear yellow gum (0·95 g.). The more volatile material

(approx. 0·2 g.) was removed by short-path distillation at 100°/1·0 mm. for 1 hr. The material which did not distil was dissolved in water (30 ml.) containing acetic acid (1·1 ml.). Potassium acetate (0·2 g.) and mercuric acetate (4·2 g.) were added and the solution was heated under reflux for 1 hr. The solution was cooled and the precipitated mercurous acetate was removed and washed with water. Additional mercuric acetate (2·0 g.) was added to the filtrate which was heated for a further 4 hr. Rubremetinium chloride (0·207 g.) was isolated from the mixture as described previously (*J.*, 1949, S 67). After crystallising twice from dilute hydrochloric acid, it was converted into the bromide and this was crystallised from very dilute hydrobromic acid to give pure (±)-*rubremetinium bromide*, m. p. 185—190° after much previous sintering. Before analysis, the material was dried at 100° in a vacuum [Found: C, 62·3; H, 5·9; N, 5·6. $C_{29}H_{33}O_4N_2Br$ requires C, 62·9; H, 6·0; N, 5·1%. Pyman (*J.*, 1914, **105**, 1591) found for (+)-rubremetinium bromide: C, 62·2; H, 6·5%].

Our sincere thanks are offered to Dr. G. D. Meakins, Chemistry Department, University of Manchester, for the infra-red absorption measurements, and to Mr. E. S. Morton for the microanalysis of (±)-rubremetinium bromide. We are also grateful to Imperial Chemical Industries Limited for grants for the purchase of chemicals.

UNITED COLLEGE, UNIVERSITY OF ST. ANDREWS. [*Received, April 10th*, 1953.]