766. *Chemical Constitution and Amœbicidal Action. Part I. Synthesis of α-Tetrahydro*isoquinolino-ω-*tetrahydro*-1-iso*quinolylalkanes Related to Emetine.*

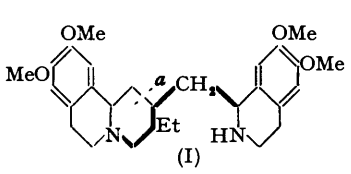
By J. M. Osbond.

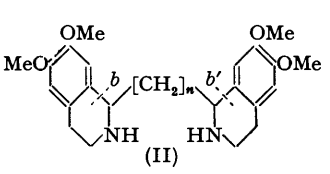
Some analogues of emetine, chiefly certain α-tetrahydro*iso*quinolino-ω-tetrahydro-1-*iso*quinolylalkanes (VIII), have been prepared which contain secondary and tertiary basic centres as present in emetine (I), in an attempt to discover what part of the emetine molecule is necessary for biological activity. These compounds have been synthesised by the route (IV) ⟶ (VIII). Although active, they do not compare favourably with emetine *in vitro*.

Emetine is unique and specific in its action on *Entamœba histolytica*, the protozoon responsible for amœbic dysentery (Dobell and Laidlaw, *Parasit.*, 1926, **18**, 206; Dobell, *Ann. Soc. belg. Med. trop., Liber Jubilaris J. Rodhain*, 1947, 201). It has the highest known activity *in vitro* of any compound which still retains its activity *in vivo* and has been used clinically for several centuries in various forms. However, although emetine still retains its pre-eminence over other drugs, there is a need for more effective and less toxic amœbicidal agents.

The correct structure for emetine (I) was put forward by Robinson (*Nature*, 1948, **162**, 524) on biogenetic grounds and confirmed independently by Battersby and Openshaw (*J.*, 1949, S59, S67, 3207) and Pailer *et al.* (*Monatsh.*, 1948, **78**, 331, 348; **79**, 127; 1949, **80**, 94) by degradative studies and by the synthesis of (±)-rubremetinium bromide (Battersby and Openshaw, *Experientia*, 1950, **6**, 378). Earlier, the preparation of analogues of emetine had been based on the old emetine formula of Brindley and Pyman (*J.*, 1927, 1067). Thus Child and Pyman (*J.*, 1929, 2010) synthesised a series of αω-bistetrahydro-1-*iso*quinolylalkanes (II; $n = 4$ and 5) and αω-bisdihydro-1-*iso*quinolylalkanes (XIII; $n = 2$, 3, and 6, R = H), but these compounds were devoid of activity. Goodson, Goodwin, Gorvin, Goss, Kirby, Lock, Neal, Sharp, and Solomon (*Brit. J. Pharmacol.*, 1948, **3**, 49) developed this line by preparing bis-[2-

(3 : 4-dimethoxyphenyl)ethylamino]alkanes (rupture of II at *b* and *b'*); several of these compounds exhibited a marked activity both *in vitro* and *in vivo*. They also prepared certain other simple compounds formally derived from emetine, of the bisalkylaminoalkane type which linked


(I)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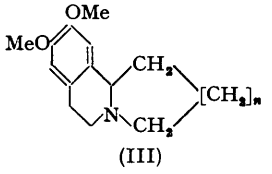
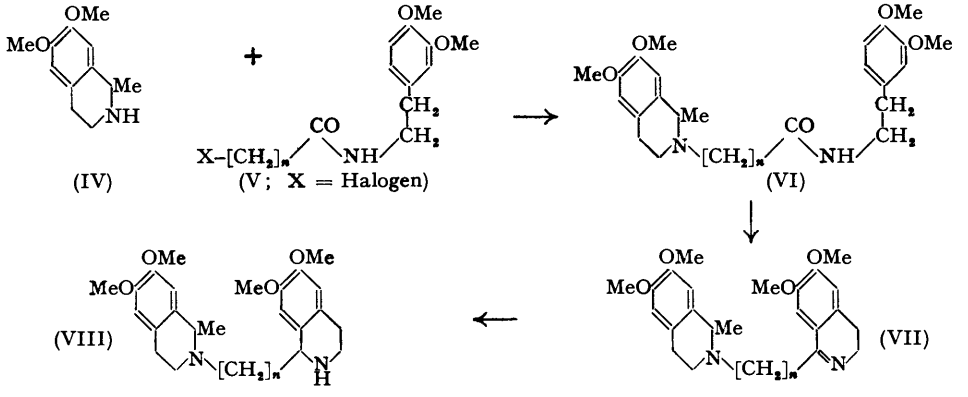

(III)

up with a series previously explored by Pyman (*J. Soc. Chem. Ind.*, 1937, **56**, 789) ending in the discovery by Pyman of bisdiamylaminodecane, which was considered to be more active *in vitro* than emetine (cf., however, Goodson and his collaborators, *ibid.*, p. 62); it was, however, not successful clinically. Child and Pyman (*J.*, 1931, 36) have also prepared the benzopyrrocoline (III; $n = 1$) and the corresponding benzopyridocoline (III; $n = 2$) which were inactive (cf. also Sugasawa *et al.*, *Ber.*, 1941, **74**, 455, 537; *Proc. Imp. Acad., Tokyo*, 1939, **15**, 82; *J. Pharm. Soc. Japan*, 1949, **69**, 85; King and Robinson, *J.*, 1938, 2119; Hall, Mahboob, and Turner, *J.*, 1950, 1842).

The present work describes the preparation of certain α-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)-ω-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)alkanes (VIII) which may be regarded as being derived from the emetine molecule (I) by rupture of the bond at *a*, thus linking the two tetrahydro*iso*quinolyl nuclei by a carbon chain, as shown in (I) by heavy bonds. These dibasic compounds contain secondary and tertiary nitrogen atoms, which are present in emetine, separated by a varying number of carbon atoms. It was felt desirable to retain the four methoxy-substituents in these analogues since these groups not only often confer enhanced biological activity but also greatly facilitate ring closure in the Bischler-Napieralski reaction.

The route chosen for the synthesis of these compounds was as shown in the scheme (IV) ⟶ (VIII). The *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-ω-halogeno-acid amides (V; $n = 1$, 2, 4, 5, or 10) were prepared by addition of the appropriate ω-halogeno-acid chloride to 2-(3 : 4-dimethoxyphenyl)ethylamine in ether (cf. Child and Pyman, *loc. cit.*, 1931). 1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinoline [IV; (±)-salsolidine] was prepared by the cyclisation of *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]acetamide with phosphoric oxide in toluene (Spath and Polgar, *Monatsh.*, 1929, **51**, 190) followed by reduction of the dihydro*iso*quinoline with palladised strontium carbonate (cf. Spath and Dengel, *Ber.*, 1938, **71**, 113); it was condensed with the ω-halogeno-amide (V) in benzene in the presence of potassium carbonate, to give *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-ω-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*-quinolino)-amides (VI; $n = 1$, 2, 4, 5, and 10). The condensation proceeded smoothly between (IV) and (V; $n = 1$, 4, 5, or 10) although in the case of (VI; $n = 5$) neither the base nor a salt could be obtained crystalline. In the preparation of (VI; $n = 2$), obtained in only moderate

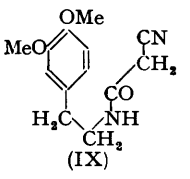

(IV) (V; X = Halogen) (VI) (VII) (VIII)

yield, it was at first difficult to obtain the pure crystalline hydrochloride and recourse was had to fractional extraction of a solution of the hydrochloride with alkali and ether. The ω-bromobutyramide (V; $n = 3$, X = Br) is not stable (cf. Child and Pyman, *loc. cit.*, 1931) and in the

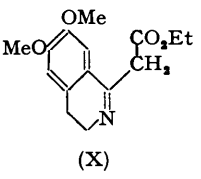
presence of moisture decomposes readily to 2-(3 : 4-dimethoxyphenyl)ethylamine hydrobromide and butyrolactone. An attempt was therefore made to prepare the bromo-amide (V; $n = 3$, X = Br) in benzene and condense it directly with (±)-salsolidine (IV). The tetrahydro*iso*quinolylbutyramide (VI; $n = 3$), however, could not be isolated, and cyclisation of the crude material by the method described below failed to give any of the required (VII; $n = 3$).

Cyclisation of *N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-β-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)propionamide and the corresponding acetamide (VI; $n = 2$ and 1 respectively) was first investigated and presented greater difficulty than that of the higher homologues (VI; $n = 4$, 5, and 10). When the propionamide derivative (VI; $n = 2$) was treated with phosphorus oxychloride in boiling toluene under the usual Bischler–Napieralski conditions, or with phosphorus pentachloride in chloroform at room temperature (Gulland and Haworth, *J.*, 1928, 581, 2083), only an amorphous product resulted from which no crystalline salt could be obtained. The acetamido-derivative (VI; $n = 1$) was also sensitive to cyclisation using the Gulland–Haworth modification at room temperature, but a small quantity of the required bis*iso*quinoline derivative (VII; $n = 1$) was obtained; when the reaction was carried out at −5° and then at 0°, a 42% yield of the desired product was obtained. Although this method was successful on two occasions, some difficulty was encountered on two subsequent runs, conducted under what were considered to be identical conditions, when a certain amount of gummy material prevented crystallisation, but after chromatography of the crude base on alumina the required salt was obtained crystalline although in diminished yield. The methane base (VII; $n = 1$) appeared to combine with only 1·5 molecules of hydrogen bromide, as did the bistetrahydro-compound derived from it by reduction. It is not unusual for dibasic compounds in a homologous series, where the two basic centres are in close proximity, to bind anomalous amounts of hydrogen halide (Mann and Watson, *J. Org. Chem.*, 1948, **13**, 502; Cook and Moffat, *J.*, 1950, 1169; Fulton, Joyner, King, Osbond, and Wright, *Proc. Roy. Soc.*, 1950, *B*, **137**, 356), and certain dihydro*iso*quinolines are known to combine with non-stoicheiometric amounts of acid (Harwood and Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 2555). The other three amides (VI; $n = 4$, 5, and 10) were, by contrast, smoothly cyclised by treatment at room temperature with phosphorus pentachloride in chloroform in good yield without complications, to give the corresponding butane, pentane, and decane derivatives respectively (VII; $n = 4$, 5, and 10).

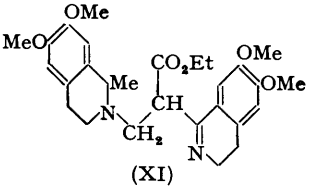
An alternative method for the synthesis of ethane derivatives such as (VII; $n = 2$) was investigated in the following way. α-Cyano-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]acetamide (IX) was cyclised to 1-cyanomethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (cf. X; CN for CO_2Et) with phosphoric oxide in toluene in 55% yield and gave on alcoholysis with hydrogen chloride and ethanol ethyl α-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)acetate (X) in almost quantitative yield. After this work had been completed the ester (X) was mentioned in a brief note by Battersby and Openshaw (*Experientia*, 1950, **6**, 378) who prepared it by a different route. When the ester (X) was treated with dilute aqueous alcoholic potassium hydroxide it was cleaved to 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline in good yield. It was considered that the CH_2 group between the two electronegative groups in the ethyl *iso*quinolylacetate (X) would be sufficiently reactive to take part in a Mannich reaction. A preliminary experiment with



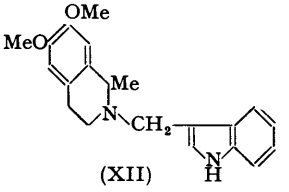
(IX)



(X)



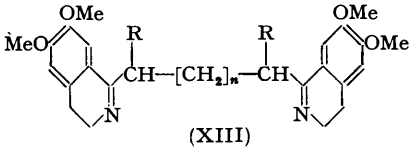
(XI)



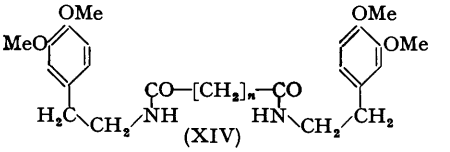
(XII)

(±)-salsolidine (IV), formaldehyde, and indole in aqueous acetic acid at room temperature gave (XII) in *ca.* 40% yield (cf. Craig and Tarbell, *J. Amer. Chem. Soc.*, 1949, **71**, 462; Kuhn and Stein, *Ber.*, 1937, **70**, 567). In similar conditions the ester (X), formaldehyde, and (±)-salsolidine (IV) gave three products: a basic oil (A) which was characterised as the dihydrobromide; a small amount of a colourless base (B), m. p. 183—185°; and a yellow base (C), m. p. 180—181°; the last two were separated with difficulty. Base (A) was considered to be ethyl α-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-β-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)propionate (XI), and hydrogenation revealed one double bond. One of the other products (B) or (C) was thought at first to be bis-(1 : 2 : 3 : 4-tetrahydro-6 : 7-

dimethoxy-1-methyl*iso*quinolino)methane (XVI) but an authentic specimen (m. p. 105—107°) prepared by condensing (±)-salsolidine and formaldehyde in aqueous acetic acid, proved to be different. These compounds were therefore derived from the ester (X) and formaldehyde. Analysis indicated that the base (B) could be ethyl αα′-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)glutarate (XIII; $n = 1$, R = CO_2Et), and this compound (B) was synthesised in good yield by condensing the ester (X; 2 mols.) with formaldehyde (1 mol.) in aqueous acetic acid. In this condensation a second compound was isolated of m. p. 158—160°, and these two isomers are presumably racemic and *meso*-forms since both gave on alkaline hydrolysis

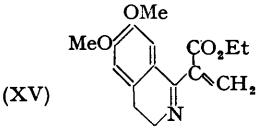


(XIII)



(XIV)

a new base (D), m. p. 162—163° (the former in 77% yield), which was shown to be 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (XIII; $n = 1$, R = H). Child and Pyman (*loc. cit.*, 1929) had previously attempted to obtain this analogue of emetine by the cyclisation of *NN′*-[2-(3 : 4-dimethoxyphenyl)ethyl]glutardiamide (XIV; $n = 3$) with phosphorus oxychloride in toluene, but, although this method had been successful with the higher homologues (XIV; $n = 4$, 5, and 8), with (XIV; $n = 3$) they obtained resinous material together with a small amount of a base [characterised as the monohydriodide, and considered to be derived from (XIV; $n = 3$) by cyclisation with loss of one molecule of water] and a quaternary salt derived from it. The cyclisation of (XIV; $n = 3$) has now been re-investigated and, although the use of phosphorus pentachloride in chloroform, which was shown to be successful with (XIV; $n = 4$), or phosphoric oxide in phosphoric acid did not give the required product, phosphoric oxide in toluene gave (XIII; $n = 1$, R = H), in 35% yield, identical with base (D) derived from base (B). After removal of a small amount of starting material, the residual gum from this cyclisation partly solidified on protracted storage, to give a second base (E), $C_{25}H_{32}O_5N_2$, in 19% yield. This base was further characterised by a monohydriodide, m. p. 134—135°. It was γ-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]butyramide [formed from (XIV; $n = 3$) by loss of $1H_2O$], although the melting point of our hydriodide differed markedly from that recorded by Child and Pyman (*loc. cit.*, 1929; m. p. 203—204°). Support for this structure was provided by treatment of base (E) with phosphoric oxide in toluene which gave 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (XIII; $n = 1$, R = H). Reduction of the propane base (XIII; $n = 1$, R = H) with tin and hydrochloric acid gave two isomers, presumably racemic and *meso*-forms of 1 : 3-bis-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (II; $n = 3$) which were separated and characterised as their dihydrobromides. It is of interest that (XIII; $n = 1$, R = H) and (II; $n = 3$) have the two *iso*quinoline nuclei linked through the 1 : 1′-positions by a chain of three carbon atoms, which are also present in the emetine molecule



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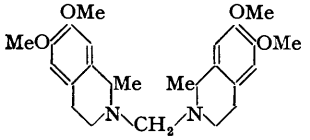
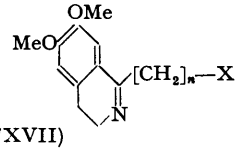


(XVI)

(I); the synthesis (X) ⟶ (XIII; $n = 1$, R = CO_2Et) ⟶ (XIII; $n = 1$, R = H) or (XIV, $n = 3$) ⟶ (XII; $n = 1$, R = H) might provide a route to still closer analogues of emetine and may merit further investigation. The third yellow base (C), which was also obtained in 71% yield by condensing the ester (X; 1 mol.) with formaldehyde (1 mol.) in aqueous acetic acid, could be either the hydroxymethyl or the methylene derivative (XV) of the ester (X) and analysis indicated that (XV) was correct. Dey and Govindachari (*Arch. Pharm.*, 1939, **277**, 177) have shown that 1-cyanomethyl-3 : 4-dihydro-6 : 7-methylenedioxy-*iso*quinoline readily yields benzylidene derivatives.

It was not thought feasible to obtain bis*iso*quinolines (VII) by condensing (±)-salsolidine (IV) directly with the appropriate 1-ω-halogenoalkyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinolines (XVII; X = halogen) since the latter class of compounds are reported to be unstable. For instance, attempts by Child and Pyman (*loc. cit.*, 1931) to condense 1-ω-chloromethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (XVII; $n = 1$, X = Cl) with ammonia or potassium

phthalimide gave only red amorphous products (cf. also Dey and Govindachari, *loc. cit.*), and our own experience showed that although the base (XVII; $n = 1$, X = Cl) was relatively stable in benzene or ether, attempts to isolate it led to red amorphous products. However, by carefully treating a benzene solution of the base or the hydrochloride of (XVII; $n = 1$; X = Cl) with an excess of piperidine 3 : 4-dihydro-6 : 7-dimethoxy-1-(piperidinomethyl)-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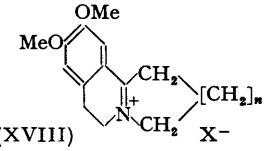
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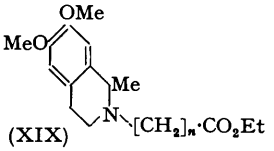
(XIX)

*iso*quinoline dihydrochloride (XVII; $n = 1$, X = $-N<[CH_2]_5$) was obtained. An attempt to condense (±)-salsolidine (IV) with the 1-chloromethyl*iso*quinoline (XVII; $n = 1$, X = Cl) in benzene in the hope of obtaining (VII; $n = 1$) led to a complex mixture from which no crystalline material could be obtained. It is interesting that the other members of this series (XVII; $n = 2$, 3, and 4, X = halogen) are equally unstable. Child and Pyman (*loc. cit.*, 1931) found that (XVII; $n = 2$, X = Cl) could not be isolated, as it was dehalogenated and polymerised during the cyclisation process (cf., however, Rajagopalan, *Proc. Indian Acad. Sci.*, 1941, **14**, *A*, 126); further (XVII; $n = 3$, X = Cl) spontaneously cyclised to (XVIII; $n = 1$, X = Cl), and (XVII; $n = 4$, X = Cl), although more stable, quaternised when warmed to give (XVIII; $n = 2$, X = Cl). The amides (V; $n = 5$ and 10, X = Br) have now been cyclised to the corresponding ω-bromopentyl- and ω-bromodecyl-3 : 4-dihydro-6 : 7-dimethoxy-*iso*quinolines (XVII; $n = 5$ and 10, X = Br) with phosphorus oxychloride in toluene. The ω-bromopentyl derivative, although more stable than the next lower homologue as might be expected, gives, when refluxed in benzene for one hour, a 34% yield of a quaternary bromide together with 40% recovery of the bromopentyl*iso*quinoline. The quaternary bromide, formulated as (XVIII; $n = 3$, X = Br) gives, on reduction with tin and hydrochloric acid, the hydrobromide of (III; $n = 3$). These two compounds, which contain seven-membered rings, represent a new type of ring system (cf. Sugasawa, Sakurai, and Sugimoto, *Proc. Imp. Acad., Tokyo*, 1939, **15**, 82).

Since, as already mentioned, the bis*iso*quinoline-propane compound (VII; $n = 3$) could not be obtained by the route (IV ⟶ VII), two alternative syntheses were attempted. Ethyl 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolinoacetate (XIX; $n = 1$), prepared by condensing (±)-salsolidine (IV) with ethyl bromoacetate in benzene in the presence of potassium carbonate, was condensed with the ester (X) in the presence of sodium ethoxide, but the only product identified was 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline. Secondly, ethyl γ-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)butyrate (XIX; $n = 3$), prepared in a similar manner from ethyl γ-bromobutyrate, was condensed with some difficulty with 2-(3 : 4-dimethoxyphenyl)ethylamine in an attempt to prepare the amide (VI; $n = 3$), which, however, could not be isolated; and cyclisation of the crude product gave no crystalline material.

Reduction of the bis*iso*quinoline-derivatives (VII; $n = 1$, 4, 5, and 10) to the α-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)-ω-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)alkanes (VIII; $n = 1$, 4, 5, and 10) was effected catalytically with Adams's catalyst in dilute hydrochloric acid at atmospheric pressure. Although by introducing a second asymmetric centre into the molecule (VII) two racemates should be obtained, in only one case (VIII; $n = 5$) were two distinct isomers isolated and characterised as dihydrogen dioxalates. In the case of the decane derivative (VIII; $n = 10$) a crystalline salt could not be obtained.

The compounds described in this communication have been tested *in vitro* against *E. histolytica* by Dr. J. D. Fulton of this Institute, using the Dobell medium containing the single organism *Bacterium coli* (Dobell, *loc. cit.*). This test has the advantage over the medium containing a mixed bacterial flora (Laidlaw, Dobell, and Bishop, *Parasit.*, 1928, **20**, 207) in that it distinguishes between direct amœbicidal action, as displayed by emetine, and indirect action caused by any bactericidal properties of the drug (cf. Fulton, Joyner, King, Osbond, and Wright, *loc. cit.*; Goodwin, Hoare, and Sharp, *Brit. J. Pharmacol.*, 1948, **3**, 44).

The most promising compound in this series was (VIII; $n = 10$) which was active at 2×10^{-6}; this was not obtained in a crystalline form but was purified by chromatography (see Experimental). Emetine, which was used as a standard in all the tests, was active at 10^{-6} to 2×10^{-7} under the same conditions. Compounds [VIII; $n = 4$ and 5 (both forms)], (VII; $n = 5$ and

10), and (XII) were active at 10^{-4}, and (VIII; $n = 1$) and (VII; $n = 4$) were active between 10^{-3} and 10^{-4}. It was found that (VI; $n = 4$ and 5), (XI), (XIII; $n = 1$, R = H), (XIII; $n = 1$, R = CO_2Et), (IIA; $n = 3$), (XVII; $n = 10$, X = Br; and $n = 1$, X = piperidino) and (X) were active at 10^{-3}; so were (VI; $n = 1$ and 2) and (XIII; $n = 2$, R = H) but these exhibited bactericidal properties at this dilution (*i.e.*, methylene-blue was not reduced). It is of interest that (IIB; $n = 3$), (XVIII; $n = 2$), (III; $n = 2$) and (XVII; $n = 5$, X = Br) were inactive. Most of the other intermediate compounds described have been tested but displayed no marked activity.

Experimental.

6-Bromo-N-[2-(3 : 4-dimethoxyphenyl)ethyl]hexanamide (V; $n = 5$, X = Br).—6-Bromohexanoyl chloride (b. p. 130°/20 mm.; 11·7 g.) in ether (30 c.c.) was added dropwise to 2-(3 : 4-dimethoxyphenyl)-ethylamine (20 g.; Bide and Wilkinson, *J. Soc. Chem. Ind.*, 1945, **64**, 84) in ether (100 c.c.) at 0° with vigorous shaking. After the addition, the mixture was allowed to warm to room temperature and, as the heavy white precipitate separated, a further quantity of ether (30 c.c.) was added to facilitate shaking. After an hour, water (100 c.c.) was added and the mixture stored at 0° overnight. The crystalline *amide* (19 g.) was collected and recrystallised from ether from which it separated in tufts of thin long needles, m. p. 70° (Found: C, 54·0; H, 6·9; N, 4·2. $C_{16}H_{24}O_3NBr$ requires C, 53·6; H, 6·75; N, 3·9%).

11-Bromo-N-[2-(3 : 4-dimethoxyphenyl)ethyl]undecanamide (V; $n = 10$, X = Br).—11-Bromoundecanoic acid (15 g.; Ashton and Smith, *J.*, 1934, 435, 1308) and thionyl chloride (25 c.c.) were heated on a water-bath for 2·5 hours. Excess of thionyl chloride was removed under reduced pressure, benzene was added, and this in turn was removed under reduced pressure. The oily acid chloride thus obtained was, without further purification (cf. Trunel, *Compt. rend.*, 1933, **197**, 453), added in ether to 2-(3 : 4-dimethoxyphenyl)ethylamine (20·5 g.) in ether (150 c.c.) at 0° with vigorous shaking. After 0·5 hour at room temperature the product was worked up as described above, the *amide* separating from benzene–light petroleum (b. p. 40—60°) in fine white needles (20·5 g.), m. p. 88—89° (Found: C, 58·8; H, 8·0; N, 3·5. $C_{21}H_{34}O_3NBr$ requires C, 58·9; H, 8·0; N, 3·3%).

1-(5-Bromopentyl)-3 : 4-dihydro-6 : 7-dimethoxyisoquinoline Hydrochloride (cf. XVII; $n = 5$, X = Br).—6-Bromo-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]hexanamide (3·55 g.) was heated under reflux with toluene (50 c.c.) and phosphorus oxychloride (15 c.c.) for 0·5 hour. The yellow solution was allowed to cool and then diluted with light petroleum (b. p. 40—60°). The supernatant liquor was decanted from the precipitated pale yellow oil which was dissolved in water and ethanol. Excess of aqueous sodium hydroxide (2N.; 70 c.c.) was added and the liberated base was extracted with ether (2 × 30 c.c.). The ethereal layer was washed with dilute hydrochloric acid (3N.; 4 × 15 c.c.), and the acid extract was taken to dryness. The *hydrochloride* separated readily from ethanol as colourless prisms (3·03 g.), m. p. 179—181° (Found: C, 51·5; H, 6·1; N, 3·8. $C_{16}H_{22}O_2NBr,HCl$ requires C, 51·0; H, 6·2; N, 3·7%), and in dilute aqueous solution exhibited a marked blue fluorescence.

1-(10-Bromodecyl)-3 : 4-dihydro-6 : 7-dimethoxyisoquinoline Hydrochloride (cf. XVII; $n = 10$, X = Br).—11-Bromo-*N*-[2-(3 : 4-dimethoxylphenyl)ethyl]undecanamide (5 g.) was heated on the water-bath with dry toluene (50 c.c.) and phosphorus oxychloride (20 c.c.) for 40 minutes. The product was worked up as in the previous experiment and the *hydrochloride* (3·6 g.) separated from ethanol–ether in large colourless cubic prisms, m. p. 144—145° (Found, on specimen dried at 100°: C, 55·4, 55·3; H, 7·5, 7·4; N, 3·2. $C_{21}H_{32}O_2NBr,HCl,0{\cdot}5H_2O$ requires C, 55·3; H, 7·5; N, 3·1%).

3 : 4-Dihydro-6 : 7-dimethoxy-1 : 2-pentamethyleneisoquinolinium Bromide (XVIII; $n = 3$; X = Br).—1-(5-Bromopentyl)-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline hydrochloride (1·18 g.) was dissolved in warm water (30 c.c.) and basified with aqueous sodium hydroxide (2N.; 20 c.c.). The precipitated oily base was extracted with ether (2 × 25 c.c.), dried (Na_2SO_4), and filtered. As the ether was removed on the steam-bath the solution became cloudy and from the residual yellow oily base some crystalline material separated out. Benzene (15 c.c.) was added and the mixture was refluxed on the water-bath for 0·5 hour. After cooling, the pale yellow needles (0·23 g.), m. p. 211—214°, which had separated were removed by filtration. The filtrate was heated for a further 0·5 hour and a further crop of crystalline material (0·13 g.) was obtained. This material was very soluble in water and gave with aqueous silver nitrate a yellow precipitate. The quaternary *bromide* separated from ethanol in hard jagged pale yellow prisms, m. p. 215—217° (Found, after air-drying: C, 49·0; H, 7·1; N, 3·3; H_2O, 13·7. $C_{16}H_{22}O_2NBr,3H_2O$ requires C, 48·7; H, 7·1; N, 3·55; H_2O, 13·7%. Found, after drying at 100°: C, 56·1; H, 6·5; N, 4·3. $C_{16}H_{22}O_2NBr$ requires C, 56·45; H, 6·5; N, 4·1%). The *picrate*, prepared by the addition of aqueous sodium picrate to a solution of the quaternary bromide, separated from ethanol in prisms, m. p. 150—151° (Found: C, 53·9; H, 5·2; N, 11·5. $C_{16}H_{22}O_2N,C_6H_2O_7N_3$ requires C, 54·1; H, 5·0; N, 11·4%). The benzene was removed from the filtrate, and from the residual gum a small amount of crystalline material slowly separated. This was dissolved in warm water, and the oily base was extracted with ether. The residue from the ethereal extract gave, when treated with dilute hydrochloric acid, a product which separated from ethanol in prisms (0·47 g.), m. p. 182°, alone or mixed with the starting material.

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1 : 2-pentamethyleneisoquinoline Hydrobromide (cf. III; $n = 3$).—The above quaternary bromide (0·14 g.) in ethanol (1 c.c.) and concentrated hydrochloric acid (1 c.c.) was heated on the water-bath, and tin foil (0·2 g.) was added in small pieces during 0·5 hour. After an hour, the alcohol was distilled off, and the solution cooled, diluted with water, and treated with hydrogen sulphide. The tin sulphide was removed and the aqueous filtrate was taken to dryness under reduced pressure. The hydrochloride could not be induced to crystallise but the *hydrobromide* separated from ethanol–ether slowly in clusters of prisms (0·08 g.), m. p. 219—220°. Recrystallisation from ethanol

gave the pure salt in fine small needle-like prisms, m. p. 220—222° (Found : C, 55·9; H, 7·0; N, 4·5. $C_{16}H_{23}O_2N$,HBr requires C, 56·1; H, 7·1; N, 4·1%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinoline [(±)-*Salsolidine*] (IV).—3 : 4-Dihydro-6 : 7-dimethoxy-1-methylisoquinoline (4·9 g.; Spath and Polgar, *loc. cit.*) in methanol (75 c.c.) was hydrogenated at room temperature (1 atm.) in the presence of palladised strontium carbonate (3 g.; 2%). When the theoretical quantity of hydrogen had been absorbed (7 hours) the catalyst was removed by filtration and the oil obtained from the filtrate, after removal of methanol, was distilled (b. p. 138—140°/0·75 mm.; 4·1 g.). The colourless viscous liquid solidified when scratched (m. p. 43—47°), and was characterised by the *hydrobromide* which separated from ethanol in clumps of needles, m. p. 174—176° (Found : C, 49·9; H, 6·2; N, 4·8. $C_{12}H_{17}O_2N$,HBr requires C, 50·0; H, 6·4; N, 4·9%). The hydrochloride separated from ethanol as fine needles in balls, m. p. 190—191° (Found : C, 59·0; H, 7·3; N, 5·5. Calc. for $C_{12}H_{17}O_2N$,HCl : C, 59·1; H, 7·4; N, 5·7%). The picrate separated from ethanol in yellow prisms, m. p. 200—201° (Spath and Dengel, *loc. cit.*, give : hydrochloride, m. p. 196—197°, and picrate, m. p. 201—201·5°).

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-α-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinolino)*acetamide Hydrochloride* (cf. VI; $n = 1$).—(±)-Salsolidine (2·07 g.), α-chloro-*N*-[2-(3 : 4-dimethoxyphenyl)-ethyl]acetamide (2·57 g.), and anhydrous potassium carbonate (2 g.) in dry benzene (10 c.c.) were heated under reflux on the water-bath for 4 hours. The mixture was cooled and water and benzene were added. The benzene layer was washed with water and with dilute hydrochloric acid (3N.; 3 × 40 c.c.). The aqueous acid extract was taken to dryness under reduced presure and ethanol was twice added to the resulting gum and then distilled off. The dry viscous residue was dissolved in ethanol, and dry ether was added just to turbidity, and next morning the hard colourless prisms which had separated in clusters (4·1 g.), m. p. 65—80°, were collected and recrystallised from ethanol–ether. The *hydrochloride* of the amide was hygroscopic and the m. p. of the air-dried specimen was indefinite owing to hydration. For analysis a specimen was dried overnight at 80° and had m. p. 92° but formed a meniscus about 100° (Found : C, 61·5; H, 7·4; N, 6·1. $C_{24}H_{32}O_5N_2$,HCl requires C, 62·0; H, 7·15; N, 6·0%). The *hydrobromide* separated from ethanol–ether in clusters of small colourless prisms and an air-dried specimen had an indefinite m. p. (90—110°) (Found : C, 54·4; H, 6·8; N, 5·4; H_2O, 3·8. $C_{24}H_{32}O_5N_2$,HBr,H_2O requires C, 54·65; H, 6·7; N, 5·3; H_2O, 3·4%). When dried at 100° it gave the anhydrous form which became glassy and brittle and then had m. p. 120° (Found : C, 56·1; H, 6·6; N, 5·4. $C_{24}H_{32}O_5N_2$,HBr requires C, 56·6; H, 6·5; N, 5·5%).

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-β-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinolino)*propionamide Hydrochloride* (VI; $n = 1$).—(±)-Salsolidine (3·09 g.), β-chloro-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]propionamide (4·05 g.), and anhydrous potassium carbonate (2·25 g.) in dry benzene (10 c.c.) were heated together on the water-bath for 4 hours. The product was worked up as described above and the resulting gum was dissolved in ethanol to which dry ether was added to turbidity. In this case crystallisation of the hydrochloride was difficult but, after seeding, the salt separated in a woolly mass of needles (4·5 g.), m. p. 158—160°. Difficulty was experienced in removing some unchanged salsolidine hydrochloride but after several recrystallisations from ethanol the m. p. was raised to 167—168°. The seed was obtained from a previous experiment where, in order to obtain a crystalline salt, it was necessary to extract the hydrochloride solution fractionally with small portions of N-sodium hydroxide and ether into 10 fractions. The base in each fraction was then converted into the hydrochloride again and from two of these fractions the *hydrochloride* eventually separated from ethanol–ether as woolly needles in wart-like clumps, m. p. 166—167° (Found : C, 63·0; H, 7·3; N, 5·6. $C_{25}H_{34}O_5N_2$,HCl requires C, 62·7; H, 7·4; N, 5·8%). Two experiments were carried out without a solvent but the yield was not so satisfactory. Attempts to cyclise the amide with phosphorus oxychloride in boiling toluene for 0·75 hour or by the action of phosphorus pentachloride in chloroform at room temperature led to an amorphous product from which no crystalline salt could be obtained.

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-δ-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinolino)*valeramide Hydrochloride* (cf. VI; $n = 4$).—(±)-Salsolidine (2·07 g.), δ-bromo-*N*-[2-(3 : 4-dimethoxyphenyl)-ethyl]valeramide (3·44 g.), and anhydrous potassium carbonate (2·5 g.) in benzene (10 c.c.) were heated on the water-bath for 4 hours. The product was worked up in the usual way and the almost colourless hydrochloride gum was dissolved in ethanol and dry ether was added to turbidity. The solution was set aside at room temperature for a week, the *hydrochloride* gradually crystallising (m. p. 115—120°). Crystallisation was slow but was aided by occasional scratching but not by chilling. The hydrochloride was recrystallised from an ethanol–ether mixture and separated in colourless very small needles (4·0 g.). An air-dried specimen had m. p. 115—120° (Found : C, 57·9; H, 7·9; N, 5·2; H_2O, 9·5. $C_{27}H_{38}O_5N_2$,HCl,3H_2O requires C, 57·8; H, 8·1; N, 5·0; H_2O, 9·6%. Found, after drying at 100° : C, 63·6; H, 7·8; N, 5·1. $C_{27}H_{38}O_5N_2$,HCl requires C, 63·9; H, 7·75; N, 5·5%). In two other experiments, one without solvent and the other without solvent or potassium carbonate, the results were not so satisfactory.

N-[2-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-11-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinolino)-*undecanamide* (VI; $n = 10$).—(±)-Salsolidine (1·03 g.), 11-bromo-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]-undecanamide (2·1 g.), and potassium carbonate (1 g.) in benzene (10 c.c.) were refluxed on the water-bath for 3 hours. A further quantity of benzene was then added and the solution was made alkaline with aqueous sodium hydroxide (2N.). After the benzene extract had been dried (K_2CO_3) and the benzene removed, the resulting gum was dissolved in ether from which the *amide* separated in colourless prisms (1·25 g.), m. p. 83—85° (Found : C, 70·9; H, 8·95; N, 5·0. $C_{33}H_{50}O_5N_2$ requires C, 71·45; H, 9·1; N, 5·05%). In a subsequent experiment under similar conditions, except that the base was first extracted with dilute hydrochloric acid, the basic amide crystallised in a different *form* from ether—as woolly needles in warts, m. p. 67—70° (Found : C, 71·25; H, 8·9; N, 5·1%). This material, however, when recrystallised in the presence of a seed of the form, m. p. 83—85°, was converted into the higher-melting solid. The hydrochloride and hydrobromide of this base could not be induced to crystallise.

(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)*methane Hydrobromide* (cf. VII; $n = 1$).—*N*-[2-(3 : 4-Dimethoxyphenyl)ethyl]-α-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)acetamide hydrochloride (1·25 g.) was dissolved in water (30 c.c.) and made alkaline by the addition of excess of 2N-sodium hydroxide. The base was extracted with benzene (2 × 25 c.c.) and dried (K_2CO_3). The colourless oil thus obtained, after removal of the benzene, was dissolved in dry chloroform and cooled to −5°. Phosphorus pentachloride (1·5 g.) was then added in one lot with shaking, and the mixture, protected from moisture, was stored at 0° for 24 hours. The solution became reddish-brown as the phosphorus pentachloride gradually dissolved and a yellow solid separated. The chloroform was removed at 30° under reduced pressure and water was then added to destroy excess of pentachloride, followed by a small quantity of ethanol to dissolve the resulting oil. The solution was made alkaline with 2N-sodium hydroxide, and the base extracted with ether (2 × 50 c.c.). The ether was extracted with 3N-hydrochloric acid (3 × 30 c.c.), and the aqueous extract taken to dryness under reduced pressure. The resulting gum, after two additions of ethanol, followed by its removal on the water-bath, was dissolved in ethanol, and dry ether was added. The dihydrochloride, after seeding, separated from the solution as small yellow tablets (0·54 g.). The dihydrochloride was an unsuitable salt, being hygroscopic with an indefinite m. p. and was therefore converted into the dihydrobromide which separated from ethanol–ether in small yellow tablets, m. p. 117—119°. For analysis a sample was crystallised from a small quantity of ethanol; it had m. p. 125° when dried at 100° (Found: C, 54·3, 54·6; H, 6·2, 6·2; N, 5·5; Br, 20·6, 22·7, 22·8, 24·6, 19·4, 22·3. $C_{24}H_{30}O_4N_2,1{\cdot}5HBr$ requires C, 54·2; H, 6·0; N, 5·3; Br, 22·5%). The halogen micro-analysis was carried out on various samples but some difficulty was met in obtaining a consistent value. For air-dried material the m. p. was indefinite, 115—120° (Found: C, 52·9; H, 6·35; N, 5·4; H_2O, 3·0. $C_{24}H_{30}O_4N_2,1{\cdot}5HBr,H_2O$ requires C, 52·4; H, 6·1; N, 5·1; H_2O, 3·3%). In two subsequent experiments under the conditions described above, *i.e.*, cooling to −5° and storage at 0° for 24 hours, the product could not at first be isolated by crystallisation owing to the presence of a red gummy impurity. However, when the crude base (2·6 g.) was chromatographed on alumina with benzene, after the first two bands (bluish under ultra-violet light) had been eluted, three fractions (total, 150 c.c. of benzene) were obtained which gave the sesquihydrobromide (0·5 g.) in pale yellow tablets from alcohol and were air-dried for analysis (m. p. 115—120°) (Found: C, 49·4; H, 6·0; N, 5·0; H_2O, 9·1. $C_{24}H_{30}O_4N_2,1{\cdot}5HBr,3H_2O$ requires C, 49·2; H, 6·3; N, 4·8; H_2O, 9·2%). The seed of the hydrochloride (m. p. 70—90°) mentioned above was obtained when the reaction was carried out at room temperature as in the above experiment. Under these conditions, however, the reaction mixture became very dark and the required salt was only obtained, in low yield, from the amorphous material by fractional extraction of the hydrochloride with N-sodium hydroxide and ether.

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)*butane Dihydrochloride* (cf. VII; $n = 4$).—*N*-[2-(3 : 4-Dimethoxyphenyl)ethyl]-δ-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)valeramide (8 g.) was dissolved in dry chloroform (40 c.c.), and phosphorus pentachloride (10 g.) was added at room temperature. Hydrogen chloride was evolved, the solution became warm, and after 1½ days the chloroform was removed and the mixture treated in the usual manner already described. The *dihydrochloride* separated readily as a crystalline powder (4·3 g.), m. p. 213—215°. Recrystallisation from ethanol afforded the pure dihydrochloride in prisms, m. p. 214—215° or 219—220° depending on the rate of heating (Found, on an air-dried specimen: C, 58·70; H, 7·3; N, 5·05; H_2O, 5·2. $C_{27}H_{36}O_4N_2,2HCl,1{\cdot}5H_2O$ requires C, 58·70; H, 7·5; N, 5·1; H_2O, 4·9. Found, on a specimen dried at 100° overnight: C, 61·7; H, 7·3; N, 5·45. $C_{27}H_{36}O_4N_2,2HCl$ requires C, 61·7; H, 7·3; N, 5·3%). The amide hydrochloride (2·72 g.) was also directly cyclised in chloroform by the same method and gave the dihydrochloride (1 g.). An attempt was made to prepare the bisquaternary methiodide by addition of methyl iodide in methanol to the bis*iso*quinoline base at room temperature. An oily quaternary salt was isolated but all attempts to crystallise it were unsuccessful. When the reactants were heated, considerable darkening of the solution occurred.

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-5-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)*pentane Dihydrobromide* (cf. VII; $n = 5$).—(±)-Salsolidine (2·27 g.), 6-bromo-*N*-[2-(3 : 4-dimethoxyphenyl)ethyl]hexanamide (3·55 g.), and potassium carbonate (anhyd.; 3 g.) were heated under reflux in benzene (15 c.c.) for 4 hours. Water and aqueous sodium hydroxide (2N.; 10 c.c.) were added and the base was extracted with benzene (2 × 25 c.c.) which was washed with water and then hydrochloric acid (3N.). Owing to the sparing solubility of the amide hydrochloride three layers were formed. The two bottom layers were run off and, on warming, a homogeneous aqueous solution was obtained. The benzene solution was extracted again with acid, and the aqueous fractions were taken to dryness. All attempts to obtain the crystalline amide hydrochloride were unsuccessful. The base amide (5·05 g.) was obtained by basification of the aqueous solution of the salt, followed by extraction with benzene (3 × 50 c.c.), as a light brown oil and was cyclised without further purification by dissolving it in dry chloroform (40 c.c.), cooling the solution to −5°, and adding phosphorus pentachloride (5 g.). The reaction mixture was left at room temperature overnight and was worked up in the manner described above. The hydrochloride of the pentane derivative could not be induced to crystallise but the *dihydrobromide* gradually separated overnight from ethanol–ether in yellow round nodules (4·8 g.), m. p. 198—200°. The pure salt separated from methanol–ether in small pale yellow prisms, m. p. 205—207°. A sample was air-dried for analysis (Found: C, 50·5; H, 6·7; N, 4·3; H_2O, 5·5. $C_{28}H_{38}O_4N_2,2HBr,2H_2O$ requires C, 50·6; H, 6·7; N, 4·2; H_2O, 5·4%).

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-10-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)*decane Dihydrogen Dioxalate* (cf. VII; $n = 10$).—The decanamide (11 g.) in chloroform (100 c.c.) was treated at 0° with phosphorus pentachloride (15 g.) and kept at room temperature overnight. The product was worked up in the manner already described, to give a gummy hydrochloride which, however, could not be induced to crystallise. Attempts to obtain the crystalline hydrobromide, hydriodide, picrate, thiocyanate, and platinum salts, and base were equally unsuccessful. The product,

however, appeared to be homogeneous since, on fractional extraction of the hydrobromide solution with 2N-sodium hydroxide (3-c.c. portions) and ether into 7 fractions, the bulk of the material was found in the 4th and 5th fractions. Eventually a *dihydrogen dioxalate* was obtained which separated from ethanol after several days in a jelly-like form but was microcrystalline under polarised light. When dried in a vacuum-desiccator over concentrated sulphuric acid it collapsed and formed a hard yellow brittle mass which softened at 95° and had m. p. 105—108° (Found: C, 60·3, 60·3; H, 7·0, 7·3. $C_{33}H_{48}O_4N_2,2H_2C_2O_4,1H_2O$ requires C, 60·5; H, 7·4%). A portion (1·85 g.) of the non-crystalline dihydrobromide obtained from the 5th fraction, in water (50 c.c.) and hydrochloric acid (3N.; 10 c.c.), in the presence of Adams's catalyst, slowly absorbed hydrogen (86 c.c. at 20°/755 mm.) overnight. No crystalline salt could be obtained, however, from this reduction, even after chromatography on alumina which, however, indicated that the product was essentially homogeneous, and this material was used in the biological test, neutralised to pH 7 by dilute hydrochloric acid.

1-*Cyanomethyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy*isoquinoline.—α-Cyano-*N*-[2-(3 : 4-dimethoxyphenyl)-ethyl]acetamide (18 g.; Child and Pyman, *loc. cit.*, 1931) was dissolved in hot toluene (200 c.c.) and to the boiling solution phosphoric oxide (60 g.) was added in two portions at intervals of 30 minutes. After the mixture had been heated under reflux for a total of 2·5 hours the hot toluene layer was decanted and, on cooling, some unchanged amide (1·1 g.) crystallised. The solid residue was carefully decomposed by the addition of water, and the yellow-brown aqueous solution was extracted with ether to remove the last traces of toluene. The acid aqueous extract was made alkaline with aqueous sodium hydroxide (50%; 100 c.c.) at 0° and the yellow crystalline precipitate was collected and recrystallised once from ethanol (450 c.c.) from which it separated in yellow prisms (9·15 g.), m. p. 170° (Child and Pyman, *loc. cit.*, 1931, give m. p. 173°).

Ethyl 3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylacetate* (X).—The cyano-*iso*quinoline (6·9 g.) was dissolved, with warming, in absolute ethyl alcohol (150 c.c.), and dry hydrogen chloride was passed into the solution for 2 hours at 0°. The mixture was stored at 0° overnight and then heated under reflux for 2 hours. The ammonium chloride was removed by filtration and the alcoholic filtrate was concentrated to 25 c.c. Water (100 c.c.) was added and the solution was made alkaline by the addition of aqueous sodium hydroxide (2N.). The yellow oil, which was extracted with ether (3 × 50 c.c.) and dried (K_2CO_3), afforded after removal of the ether the ester (7·2 g.) in crystalline form when left under light petroleum (b. p. 40—60°) overnight. The ester was recrystallised from light petroleum (250 c.c.) from which it separated in hard yellow prisms in clusters in two *forms*, yellow needle-like prisms in clumps, m. p. 80—82° (Found: C, 64·9; H, 6·7; N, 5·6. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·8; N, 5·1%), and cubic prisms m. p. 86—87° (Found: C, 65·1; H, 6·4; N, 4·9%). Battersby and Openshaw (*Experientia, loc. cit.*) give m. p. 85·5—86·5°. The *picrate* separated from ethanol, in which it was sparingly soluble, in yellow needles, m. p. 170—171° (Found: C, 49·9; H, 4·2; N, 11·3. $C_{15}H_{19}O_4N,C_6H_3O_7N_3$ requires C, 49·8; H, 4·4; N, 11·1%). The *hydrobromide* separated from ethanol–ether as large yellow prisms. It sintered at 155° and had m. p. 160° (decomp.) (Found, in air-dried specimen: C, 49·4; H, 5·6; N, 3·8; H_2O, 3·0. $C_{15}H_{19}O_4N,HBr,0·5H_2O$ requires C, 49·1; H, 5·75; N, 3·8; H_2O, 2·45%).

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinoline.—Ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate (0·35 g.) was refluxed on the water-bath with alcoholic potassium hydroxide (5%; 10 c.c.) for 0·5 hour. Water (10 c.c.) was added and the alcohol was allowed to distil off (0·5 hour). The base was extracted with benzene, washed with water, and dried (K_2CO_3). The benzene extract was concentrated and light petroleum was added. The large prisms, m. p. 102—103°, that separated were recrystallised from benzene–light petroleum, to give the dihydro*iso*quinoline (0·25 g.) in prisms, m. p. and mixed m. p. with an authentic specimen, 103—104° (Found: N, 6·4. Calc. for $C_{12}H_{15}O_2N$: N, 6·8%); the picrate had m. p. 209—211°. Spath and Polgar (*loc. cit.*) give m. p. 106—107°, and picrate m. p. 210—212°.

Ethyl α-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-β-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*-iso*quinolino*)*propionate Dihydrobromide* (cf. XI).—(±)-Salsolidine (1·03 g.) and ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate (1·38 g.) were dissolved in aqueous acetic acid (50%; 10 c.c.) with warming. Formalin (40%; 0·5 c.c.) was added and the solution left at room temperature for 20 hours. Water was added and the solution, after extraction with ether, was made alkaline with excess of sodium hydroxide solution (2N.), and the bases were extracted with ether. The viscous yellow oil, obtained after removal of the ether, triturated with a little alcohol and cooled to 0°, gave a yellow granular deposit (0·5 g.) which separated from benzene in large yellow rectangular prisms, m. p. 156—180°. After three recrystallisations from benzene, base (C), m. p. 180—181°, was obtained which gave no depression of the m. p. on admixture with *ethyl* α-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*acrylate* (see below) (Found: C, 66·8; H, 7·0; N, 5·0. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6; N, 4·8%). From the benzene mother-liquors a second compound was isolated in small yield and after several recrystallisations from benzene gave colourless prisms, base B; the m. p. and mixed m. p. with ethyl αα′-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-isoquinolyl)glutarate was 183—185°. A mixed m. p. with base (C) gave a depression to 165—175°. When this material was treated with hot aqueous alcoholic potassium hydroxide for 0·5 hour on the water-bath (see below) a new base (D) was obtained which separated from alcohol in fine needles, m. p. and mixed m. p. with 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane 159—161°. To the alcoholic mother-liquor after removal of bases (B) and (C) was added hydrobromic acid (N.; 6 c.c.), the solution was taken to dryness, and the residue was dissolved in ethanol from which the *dihydrobromide* separated slowly on the addition of ether as yellow prisms (0·55 g.), m. p. 163—170° (decomp.). After three recrystallisations from ethanol the pure salt was obtained in clumps of prisms, m. p. 174—175° (decomp.) (melted to a red liquid with evolution of small bubbles), and gave a depression when admixed with (±)-salsolidine hydrobromide to 170—173°; when air-dried a specimen, had m. p. 172—174° (decomp.) (Found: C, 50·2; H, 6·4; N, 4·4; H_2O, 0·8. $C_{28}H_{36}O_6N_2,2HBr,0·5H_2O$ requires C, 50·3; H, 6·2; N, 4·2; H_2O, 1·3%). The dihydrochloride separated from ethanol–ether in

clumps of prisms, m. p. 173—175° (decomp.). The dihydrobromide (0·41 g.) in dilute hydrochloric acid was reduced in the presence of Adams's catalyst at atmospheric pressure and slowly absorbed 20 c.c. of hydrogen (theoretical, 15 c.c.) overnight. A crystalline hydrobromide could not be obtained from the reduction mixture.

1 : 2 : 3 : 4-*Tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*-1-*methyl*isoquinoline (XII).—(±)-Salsolidine (1·03 g.), indole (0·58 g.), and formaldehyde (40%; 0·5 c.c.) in aqueous acetic acid (50%; 10 c.c.) were set aside at room temperature for 2 days. The solution was made alkaline with sodium hydroxide solution (2N.), and the basic material was extracted with ether and dried (K_2CO_3). After removal of the ether the resulting gum was dissolved in ethanol–ethyl acetate, and light petroleum was added with scratching. A crystalline solid (0·84 g.) slowly separated, having m. p. 125—130° which, after recrystallisation from benzene–light petroleum (b. p. 40—60°) and then twice from *iso*propyl alcohol, gave the pure *base* in clusters of prisms (0·35 g.), m. p. 135—137° or 139—141° depending on the rate of heating (Found: C, 74·8; H, 7·3; N, 8·4. $C_{21}H_{24}O_2N_2$ requires C, 75·2; H, 6·9; N, 8·35%). A solution of the base in dilute hydrochloric acid gradually became violet.

Ethyl α-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*acrylate* (XV).—Ethyl (3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)acetate (1·1 g.; 1 mol.) and aqueous formaldehyde (0·6 c.c.; 20%; 1 mol.) in aqueous acetic acid (10 c.c.; 50%) were kept at room temperature for 19 hours. The solution was made alkaline by the addition of sodium hydroxide solution (2N.), and the basic material was extracted with chloroform (2 × 40 c.c.), washed with water, and dried (K_2CO_3). After removal of the chloroform, the residue was dissolved in a small volume of benzene and diluted with twice its volume of dry ether. The hard yellow cubic prisms (0·81 g.), m. p. 175—179°, were collected and recrystallised from benzene and then had m. p. 179—181° alone or mixed with base C obtained in the Mannich reaction between the ester (X) and (±)-salsolidine as described above.

Ethyl αα′-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*glutarate* (XIII; R = CO_2Et, *n* = 1).—Ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate (1·1 g.; 2 mols.) and aqueous formaldehyde (0·3 c.c.; 20%; 1 mol.) in aqueous acetic acid (10 c.c.; 50%) were kept at room temperature for 19 hours. The solution was made alkaline with excess of sodium hydroxide solution (2N.), and the basic material was extracted with chloroform (2 × 40 c.c.), washed with water, and dried (K_2CO_3). The *base*, after removal of the chloroform, when treated with benzene and ether gave colourless prisms (0·54 g.), m. p. 178—182°, which separated from benzene in hard colourless prisms, m. p. 182—183° (Found: C, 65·5; H, 6·4; N, 4·7. $C_{31}H_{38}O_8N_2$ requires C, 65·7; H, 6·7; N, 4·9%). This material gave, as described below, on alkaline hydrolysis 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane, m. p. 162—163°. From the mother-liquor a microcrystalline solid (0·1 g.), m. p. 150—160° gradually separated out at 0° and, after two recrystallisations from benzene–ether, the second, isomeric *base* had m. p. 157—161° (Found: C, 65·4; H, 6·9. $C_{31}H_{38}O_8N_2$ requires C, 65·7; H, 6·7%). This isomer also gave, when treated with aqueous alcoholic potassium hydroxide (5%), 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane, m. p. and mixed m. p. 158—159°.

1 : 4-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*butane* (XIII; *n* = 2; R = H).—*NN′*-[2-(3 : 4-Dimethoxyphenyl)ethyl]adipdiamide (3 g.) was dissolved in dry chloroform (25 c.c.), and phosphorus pentachloride (6 g.) was added in one lot with shaking. Hydrogen chloride was evolved and the reaction mixture cooled and then set aside at room temperature for 12 hours, whereupon a yellow granular deposit separated. The chloroform was removed under reduced pressure, the residue was dissolved in ethanol, and the solution made alkaline with sodium hydroxide solution. After dilution of this solution with water the felted needles that separated were collected and crystallised from ethyl acetate as needles (0·8 g.), m. p. 170—171° (Child and Pyman, *loc. cit.*, 1929, give m. p. 172—173°).

1 : 3-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*propane* (XIII; *n* = 1; R = H).—(*a*) To a solution of *NN′*-[2-(3 : 4-dimethoxyphenyl)ethyl]glutardiamide (5 g.) in boiling dry toluene (100 c.c.) was added phosphoric oxide (15 g.) in one lot with constant shaking, and after an hour a further portion of phosphoric oxide (5 g.) was added. After the mixture had been refluxed for a total of 2·75 hours the toluene layer was decanted whilst hot and the residual cake, after cooling, was cautiously decomposed with water. The toluene layer was separated and the aqueous layer was extracted once with ether and then made strongly alkaline with aqueous sodium hydroxide (50%). The yellow oil which separated gave, when scratched and cooled to 0°, a partly solid material which was collected, washed with water, and dissolved in a minimum quantity of ethanol. The *base* separated in a mass of felted needles (1·6 g.), m. p. 159—161° (Found: C, 70·8; H, 7·2; N, 6·5. $C_{25}H_{30}O_4N_2$ requires C, 71·05; H, 7·2; N, 6·6%). The *dihydrobromide* separated from ethanol as pale yellow prisms which, when air-dried, softened at 214° with m. p. 216—218° (Found: C, 50·0; H, 5·4; H_2O, 3·0. $C_{25}H_{30}O_4N_2$,2HBr,1H_2O requires C, 49·8; H, 5·7; H_2O, 3·0%). When dried at 130° it became anhydrous (Found: N, 4·9. $C_{25}H_{30}O_4N_2$,2HBr requires N, 4·8%). The dihydrochloride separated from ethanol in thick rod-like prisms, m. p. 195—205° (decomp.). The alcoholic mother-liquors were combined, the ethanol was removed, and the residue taken up in benzene and cooled at 0°. The white felted needles (0·36 g.) which separated proved to be unchanged starting material, m. p. and mixed m. p. 128—130°. The filtrate was concentrated and on protracted storage a crystalline solid formed in the residual gum. It was removed and crystallised from benzene from which it separated in transparent prisms (0·9 g.), m. p. 135° (Found: C, 68·25; H, 7·0; N, 6·45. $C_{25}H_{32}O_5N_2$ requires C, 68·15; H, 7·3; N, 6·4%). This base was considered to be γ-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-*N*-[2-(3 : 4-*dimethoxyphenyl*)*ethyl*]*butyramide* and it gave a *monohydriodide* which separated from methanol as yellow needles, m. p. 133—135° (Found: C, 52·9; H, 5·8; N, 5·0. $C_{25}H_{32}O_5N_2$,HI requires C, 52·8; H, 5·85; N, 4·9%). When the basic amide (79 mg.) was dissolved in boiling dry toluene (5 c.c.) and treated with phosphoric oxide (0·5 g.) and heated at 120° (oil-bath) for 2 hours it gave, after being worked up as described above, 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane, which separated from benzene and then from ethanol as a mass of fine colourless needles (20 mg.), m. p. and mixed m. p. 161—162°.

(*b*) Ethyl *aa'*-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)glutarate (0·35 g.) (XIII; $n = 1$, R = CO_2Et) was refluxed on the water-bath with alcoholic potassium hydroxide (10 c.c.; 5%) for 0·5 hour. The white solid which separated dissolved on addition of water (2 c.c.). After a further 0·5 hour's heating more water (*ca.* 10 c.c.) was added and most of the alcohol was allowed to distil off. On cooling, the yellow oil, which crystallised when scratched to fine needles, was collected and crystallised from ethanol as a mass of fine felted needles (0·2 g.), m. p. 162—163° alone or mixed m. p. with the bis*iso*quinolylpropane obtained in (*a*).

1 : 3-*Bis*-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*propane Dihydrobromides* (cf. II; $n = 3$). —To a boiling solution of 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (0·56 g.) in ethanol (2·5 c.c.) and concentrated hydrochloric acid (2·5 c.c.), tin (1·5 g.) was added and the mixture was refluxed for 4 hours with a further addition of acid (1 c.c.) after 1 hour. The alcohol was distilled off, and the solution was diluted with water and treated with hydrogen sulphide. The sulphide was removed by filtration and washed with warm water. The filtrate was made alkaline with aqueous sodium hydroxide (50%), and the basic material extracted with ether. After removal of the ether the residue was dissolved in a small quantity of alcohol but no crystalline base could be obtained. A small amount of amorphous material was removed and the filtrate treated with excess of hydrobromic acid (2N.) and taken to dryness. The *dihydrobromide* A separated from ethanol readily in needle-like prisms (0·21 g.), m. p. 268—270°, and then from methanol as colourless needles, m. p. 270—272° with shrinking at 267° (Found, in material dried at 130° : C, 51·4; H, 6·4; N, 5·0. $C_{25}H_{34}O_4N_2$,2HBr requires C, 51·0; H, 6·2; N, 4·8%). To the alcoholic mother-liquor ether was added and after several days a second isomer separated in round clumps (hemispherical) (0·13 g.), m. p. 240—243°, together with some feathery needles of the first isomer (m. p. 265°). The *dihydrobromide* B separated from methanol as fine needles in bundles, m. p. 237—239° (Found, on air-dried sample : C, 50·5; H, 6·1; H_2O, 1·6. $C_{25}H_{34}O_4N_2$,2HBr,0·5H_2O requires C, 50·3; H, 6·2; H_2O, 1·5%).

Bis-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)*methane* (XVI).—(±)-Salsolidine (1·03 g.) and aqueous formaldehyde (0·25 c.c.; 40%) were condensed in aqueous acetic acid (20 c.c.; 25%) at 100° for an hour. The solution was made alkaline and the base was extracted with ether and dried (K_2CO_3). The clear colourless oil, obtained by removal of the ether, was scratched in benzene–light petroleum (b.p. 40—60°), and cooling to 0° gave a solid. The *base* separated from benzene–light petroleum (b. p. 40—60°) as hard colourless prisms (0·3 g.), m. p. 105—107° (Found : C, 70·1; H, 8·2; N, 6·6. $C_{25}H_{34}O_4N_2$ requires C, 70·4; H, 8·0; N, 6·6%).

(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*methane Hydrobromide* (cf. VIII; $n = 1$).—(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinolino)methane hydrobromide (0·57 g.) was dissolved in water (30 c.c.) and dilute hydrochloric acid (3N.; 5 c.c.) and hydrogenated at 1 atmosphere and room temperature in the presence of Adams's catalyst. The absorption of hydrogen was rapid at first but soon became slower and after overnight shaking 36 c.c. were absorbed (temp. = 18°). The catalyst was removed by filtration and the filtrate taken to dryness under reduced pressure. An excess of hydrobromic acid (2N.) was added; the *sesquihydrobromide* separated from ethanol–ether as a micro-crystalline powder (0·3 g.). The salt crystallised from ethanol in small well-defined colourless prisms which after drying at 100° had m. p. 130—132° with the meniscus forming at 140° (Found, on air-dried sample : C, 49·3; H, 6·5; N, 5·3; H_2O, 8·8; Br, 20·3. $C_{24}H_{32}O_4N_2$,1·5HBr,3H_2O requires C, 49·0; H, 6·8; N, 4·8; H_2O, 9·2; Br, 20·4%). No crystalline material could be obtained from the mother-liquors.

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*butane Dihydrogen Dioxalate* (cf. VIII; $n = 4$).—The corresponding propane dihydro*iso*quinoline dihydrochloride (0·52 g.) in water (30 c.c.) and dilute hydrochloric acid (3N.; 5 c.c.) was hydrogenated in the presence of Adams's catalyst (0·1 g.). After overnight shaking the catalyst was removed and the filtrate, which was no longer fluorescent under ultra-violet light, was taken to dryness. Attempts to crystallise the dihydrochloride were unsuccessful. The base, however, obtained by addition of aqueous sodium hydroxide to the salt solution and extraction with ether (2 × 50 c.c.), gave when treated with oxalic acid (anhyd.; 0·2 g.) a *dihydrogen dioxalate* as an amorphous powder (0·4 g.), m. p. 125—120° with the meniscus forming at 160°. The salt after several crystallisations from ethanol, from which it separated very slowly during several days in small nodules of woolly needles, was obtained pure (0·26 g.) with m. p. (of air-dried specimen) 90—130° (Found : C, 54·75; H, 6·9; N, 4·5; H_2O, 6·4. $C_{27}H_{38}O_4N_2$,2$H_2C_2O_4$,2·5H_2O requires C, 54·8; H, 7·0; N, 4·1; H_2O, 6·6%). A sample dried at 110° had m. p. 140—145° (Found : C, 59·2; H, 7·3; N, 4·8. $C_{27}H_{38}O_4N_2$,2$H_2C_2O_4$ requires C, 58·7; H, 6·8; N, 4·4%).

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinolino*)-5-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*pentane Dihydrogen Dioxalates* (cf. VIII; $n = 5$).—The corresponding pentane dihydro*iso*quinoline dihydrobromide (1·2 g.) in water (60 c.c.) and dilute hydrochloric acid (3N.; 10 c.c.) was hydrogenated in the presence of Adams's catalyst (0·06 g.). Absorption of hydrogen was rapid at first and the theoretical quantity was absorbed after 4 hours. After the catalyst had been removed, the filtrate was made alkaline with aqueous sodium hydroxide (2N.; 30 c.c.), and the base extracted with ether (2 × 50 c.c.). After removal of the ether, the base was dissolved in ethanol (30 c.c.), and oxalic acid (0·55 g.) in ethanol (10 c.c.) was added. A white crystalline material (0·72 g.), m. p. 184—189°, slowly separated overnight at 0°. The *dihydrogen dioxalate* A, which was sparingly soluble in ethanol, separated from methanol in colourless cubic prisms, m. p. 192—194° (Found : C, 59·5; H, 6·9; N, 4·4. $C_{28}H_{40}O_4N_2$,2$H_2C_2O_4$ requires C, 59·2; H, 6·8; N, 4·3%). From the mother-liquor on concentration a second racemate was obtained, on long storage, as large prisms (0·33 g.), m. p. 153—155°. This *dihydrogen dioxalate* B separated from methanol–ether in small colourless prisms, m. p. 150—152° (Found, in air-dried specimen : C, 56·9; H, 6·85; N, 4·3; H_2O, 4·6. $C_{28}H_{40}O_4N_2$,2$H_2C_2O_4$,1·5H_2O requires C, 57·0; H, 7·0; N, 4·1; H_2O, 4·0%).

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*piperidinomethyl*isoquinoline *Dihydrochloride* (cf. XVII; X = piperidino).—To 1-chloromethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline hydrochloride (3·0 g.) piperidine (20 c.c.) was added with vigorous shaking and warming on the water-bath for 10 minutes. The mixture was then heated at 95° for 2 hours. Water and chloroform were then added together with excess of 2N-sodium hydroxide, and the chloroform layer separated. After the chloroform and excess of piperidine had been removed under reduced pressure, the red gummy residue was treated with excess of 2N-hydrochloric acid, and the solution was taken to dryness. The *dihydrochloride* (1·78 g.) sintered at 165°, had m. p. 180° (decomp.), separated from ethanol in flat square yellow prisms and after two recrystallisations sintered at 150° and melted at 195—198° (decomp.) (Found : C, 56·45; H, 7·2; N, 7·6. $C_{17}H_{24}O_2N_2$,2HCl requires C, 56·5; H, 7·25; N, 7·75%).

***Attempted Condensation between* 1-*Chloromethyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy*isoquinoline *and* (±)-*Salsolidine*.**—(±)-Salsolidine (2·07 g.; 2 mols.) was added to an ethereal solution of the chloro-base [derived from the hydrochloride (1·37 g.; 1 mol.) by treatment with sodium carbonate and ether] and after the ether had been distilled off benzene (15 c.c.) was added and the solution was heated on the water-bath for 2 hours. Crystals separated in the first few minutes and these were collected (0·84 g.) and recrystallised from ethanol, to give (±)-salsolidine hydrochloride, m. p. 188—190°. No crystalline salt could be isolated from the mother-liquor (green), and the crude base when chromatographed on alumina in benzene showed at least 9 bands. No crystalline material could be isolated from any of these bands.

Ethyl* 1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinolinoacetate *Hydrobromide (cf. XIX; $n = 1$).—(±)-Salsolidine (2·07 g.), ethyl chloroacetate (1·22 g.), and anhydrous potassium carbonate (1·5 g.) were refluxed in benzene (5 c.c.) for 3 hours. Water was added and the base was extracted with benzene and dried (K_2CO_3). Distillation of the residue gave a pale yellow viscous oil (2·06 g.) (b. p. 180°/0·5 mm.), the *hydrobromide* of which separated from ethanol in prisms, m. p. 186—188° (decomp.) (Found : C, 51·3; H, 6·3; N, 3·7. $C_{16}H_{23}O_4N$,HBr requires C, 51·3; H, 6·5; N, 3·7%).

Ethyl* γ-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*isoquinolino)*butyrate* *Hydrobromide (XIX; $n = 3$).—This was prepared in a similar way, from (±)-salsolidine (2·07 g.), ethyl γ-bromobutyrate (1·95 g.), and potassium carbonate (1·5 g.) in benzene (15 c.c.). The *hydrobromide* (1·65 g.), m. p. 164—165°, separated from ethanol in fine white needles (Found : C, 53·7; H, 7·3; N, 3·5. $C_{18}H_{27}O_4N$,HBr requires C, 53·75; H, 7·0; N, 3·5%). An attempt was made to condense the base with 3 : 4-dimethoxyphenylethylamine at 180° and at 200—210° for 7 hours. Under the former conditions half of the propionate was recovered unchanged and under the latter the reaction mixture became rather dark and tarry. An attempt was made to cyclise the crude amide, which could not be crystallised, but no useful product resulted.

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