RESEARCH PAPERS

THE SYNTHESIS OF CERTAIN BIS*ISO*QUINOLINE DERIVATIVES STRUCTURALLY RELATED TO EMETINE

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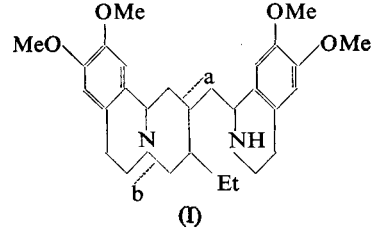
Received March 20, 1957

α ω-Bis(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-propane,-butane, and -2- methylpropane have been prepared, the latter for the first time and the structures confirmed by comparing the ultra-violet light spectrophotometric measurements with those for ethyl γ-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*-quinolyl) butyrate. The prepared compounds have been hydrogenated to give the corresponding tetrahydro*iso*quinoline derivatives and the structures confirmed by spectrophotometric measurements and by comparison of the pKa values with those of the corresponding dihydrocompounds. The tetrahydro*iso*quinoline derivatives are of comparable basic strength with emetine. Biological results are not yet available. An alternative route to the necessary amides required as intermediates for the above has been found to yield amides free from the unwanted cyclic imides, but the yields are not as good as by the other route. The use of a potassium bisulphate sodium sulphate mixture for ring-closing the amides has been found to yield cyclic imides instead of the required *iso*quinoline derivatives.

UNTIL the structure of emetine was successfully established by Robinson[1] and confirmed by the work of Battersby and Openshaw[2] the preparation of synthetic analogues had been based on a structure proposed by Brindley and Pyman[3].

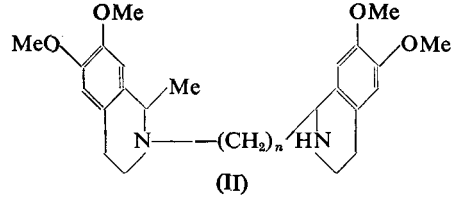
Emetine (I) has been synthesised by Preobrazhenskii[4] and many



(I)

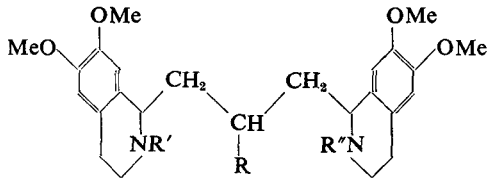
synthetic analogues, based on this structure have been prepared[5–8], some of which show marked activity against *Entamoeba histolytica*.

Osbond[7] first prepared a series of α-tetrahydro-*iso*quinolino-ω-tetrahydro-1-*iso*quinolylalkanes (II, $n = 1, 4, 5$ and 10) which may be regarded



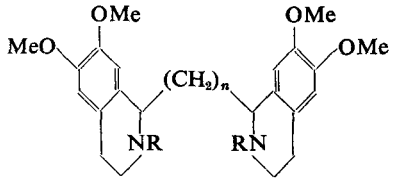
(II)

as being derived theoretically from emetine by rupture at the dotted line "a" (I). *In vitro* activity against *E. histolytica* was shown by a concentration of $1:10^4$ whereas, under the same conditions emetine was active at $1:10^6$. A second series prepared by Osbond[8] were the bistetrahydro*iso*quinolylalkanes (III), R = Et, Pr, R′, R″ = H or Me), recalling to



(III)

mind the straight-chain *iso*quinolylalkanes (IV) prepared by Child and Pyman[9] in 1929.



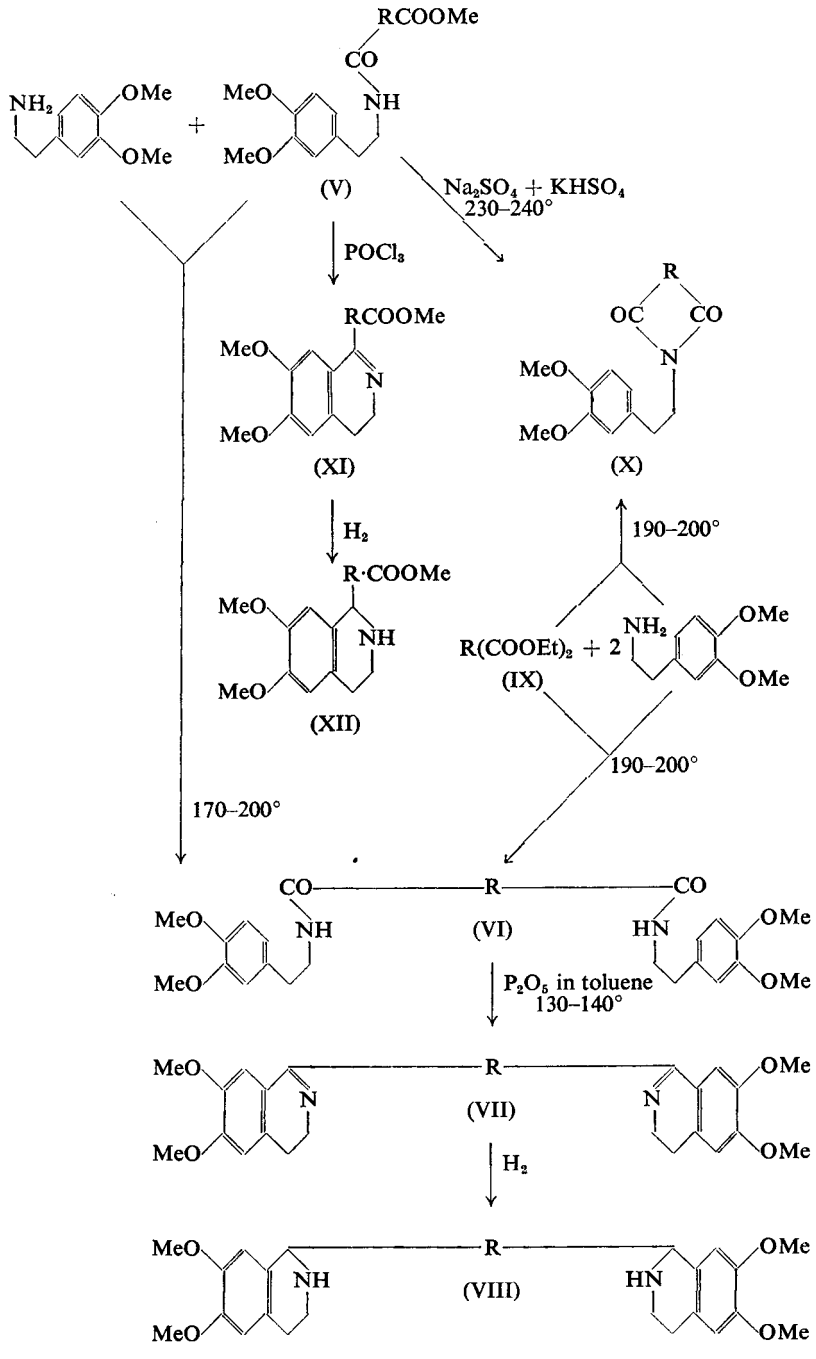
(IV, n = 4, 5, 8; R = H, Me)

In Osbond's second series the activity (*in vitro*) depended very much on the natures of the groups R, R′ and R″ and in those compounds where R′ and R″ were different no activity was observed at concentrations as low as $1:10^4$. In the structurally symmetrical compounds activity was observed when R′ = R″ = H and R = Et. Two "Racemates" of this structure were isolated (one of these would, of course, be a "meso" form and not a racemate). "Racemate A" was inactive but "Racemate B" was active at a concentration of $1:10^3$. When R′ = R″ = H but R = propyl instead of ethyl the activity increased and both "racemates" were active at concentrations as low as $1:10^4$.

The same sort of activity was obtained when R′ = R″ = Me and R = Et, but if R = Pr and R′ and R″ = Me the activity disappears. All these compounds may be theoretically derived from emetine by rupturing the molecule I at "b".

In view of the above results it seemed desirable to prepare further compounds of this nature and as methylation of the two *N* atoms appears not to enhance amoebecidal activity it was decided to keep R′, and R″ = H and to concentrate on varying R in the structure III. The nearest approach to emetine would be obtained by making R = CH(Me)(Et) but it was decided to commence with R = Me followed by R = $CH(Me)_2$ and also to prepare certain of the "straight chain" (R = H) compounds prepared by Child and Pyman (IV, n = 3, 4, R = H) in order to make a comparative study of the physico-chemical data.

The compounds were prepared according to the scheme shown overleaf.



R = $(CH_2)_3$; $(CH_2)_4$, *iso*Pr; $(CH_2{-}CH{-}CH_2)$ *iso*Pr.

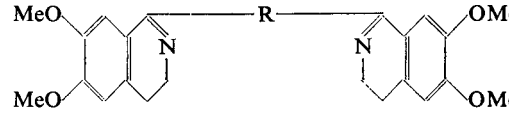
The rather longer route to the diamides (VI) by way of the amido esters (V) was investigated as the route followed by Child and Pyman[9] and Osbond[8] yielded the cyclic imides (X) as by-products. However, although the former route yielded diamide free from imide the increase in the yield was not sufficiently great to justify the more lengthy synthesis of the amide esters (V) against that of the simple esters (IX) (five stages instead of one).

Child and Pyman[9] ring-closed the diamides of the type VI (R = $(CH_2)_n$ where $n = 4, 5, 8$) by means of phosphorus oxychloride to yield the corresponding bis*iso*quinolines (VII) but were unable to isolate any product with the corresponding succinamide (VI, R = $-(CH_2)_2-$) and obtained anomalous results with the glutaramide (R = $-(CH_2)_3-$). After we failed to obtain ring-closure with the same reagent or with polyphosphoric acid or hydrofluoric acid, we applied the reagent consisting of a mixture of potassium hydrogen sulphate (4 parts) and anhydrous sodium sulphate (1 part) at 230–240°, first used by Baddar and Gindy[10].

TABLE I

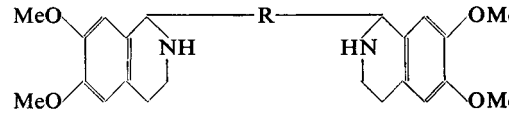
ULTRA-VIOLET LIGHT ABSORPTION OF DIHYDRO- AND TETRAHYDRO-*iso*QUINOLINES

1. Dihydro-*iso*quinolines



Reference No.	R =	λ max in mμ	ε	Log ε
XI	$-(CH_2)_3COOEt$ (base) (one *iso*quinoline ring)	244 303	15,080 8,412	4·1784 3·9249
VIIa	$-CH_2\cdot CH(Me)CH_2-$ (Dihydrochloride)	243 304	28,210 16,390	4·4504 4,2146
VIIb	$-(CH_2)_4-$ (base)	243 302	27,960 16,530	4·4465 4·2183
VIIc	$-(CH_2)_5-$ (base)	243 304	29,890 17,140	4·4755 4·2340

2. Tetrahydro-*iso*quinolines



Reference No.	R =	λ max in mμ	ε	Log ε
XII	$-(CH_2)_3COOEt$ (hydrochloride) (one *iso*quinoline ring)	230 282	7,598 3,864	3·881 3·587
VIIIa	$-CH_2\cdot CH(Me)CH_2-$ (hydrochloride)	230 282	13,740 6,237	4·138 3·795
VIIIb	$-(CH_2)_4-$ (base)	228 282	15,040 9,137	4·177 3·819
VIIIc	$-(CH_2)_5-$ (dihydrochloride)	229 282	12,540 5,282	4·098 3·722

The desired bis*iso*quinolines were not obtained; no one appears yet to have prepared *iso*quinolylethane, VII, (R = $-(CH_2)_2-$). The compounds actually obtained were the corresponding imides (X, R = $-(CH_2)_2-$, $-(CH_2)_3-$, etc.). Finally, in all cases (except that of the succinamide) the desired bis*iso*quinolylalkanes were obtained by following Osbond's method using P_2O_5 in toluene.

The tetrahydro*iso*quinolines (VIII) were prepared from the corresponding dihydro-derivatives (VII) by hydrogenation at room temperature and pressure in the presence of Adams' platinum oxide catalyst.

1:3-Bis(3:4:-dimethoxy-1:2:3:4-tetrahydro-1-*iso*quinolyl)-β-methyl propane (III, R = CH_3) which could not be obtained solid was characterised as its hydrochloride and by comparing its ultra-violet light absorption curve with that of known compounds, (III, R = H, and VIII, R = $(CH_2)_4$), and with that of ethyl-γ-(6:7-dimethoxy-1:2:3:4-tetrahydro-1-*iso*quinolyl)butyrate. Further evidence that hydrogenation had occurred as required was supplied by a study of the pKa values of the bisdihydro and the bistetrahydro-compounds respectively (see Table II). The corresponding *iso*propyl compound (III, R = $CH(Me)_2$) was not obtained, analysis and absorption data showing that the dihydro compound (VII, R = CH_2–CH(*iso*Pr)CH_2) had not been obtained in a pure condition. A dipicrate with a satisfactory analysis for the required compound was obtained pure after several recrystallisations, but only in small yield.

TABLE II

EFFECT OF HYDROGENATION ON THE BASIC STRENGTHS OF CERTAIN DIHYDRO*iso*QUINOLINES

(For Formulae of Compounds see Table I)

Before hydrogenation		After hydrogenation	
Reference No. of compound	pKa	Reference No. of compound	pKa
XI	7·4	XII	8·3
VIIa	6·8	VIIIa	8·2
VIIc	6·8	VIIIc	8·2

Dissociation constants for emetine—$pKa_1 = 8{\cdot}2$, $pKa_2 = 7{\cdot}4$

The tetrahydro compounds are comparable in basic strength with emetine itself, probably one of the prerequisites for amoebicidal activity. Those prepared for the first time (VIII, R = $CH_2CH(Me)CH_2$, and XII, R = $(CH_2)_3COOEt$) have been submitted for biological testing.

EXPERIMENTAL

(The micro analyses were made by Mr. G. Crouch of these laboratories.) Melting points are uncorrected.

γ-Carbethoxybutyryl Chloride

This was obtained in 84 per cent yield by the method of Clark[11] b.p. 75–76°/1·4 mm. p-*Toluidide* m.p. 98–99°. Found: C, 67·7; H, 7·6; N, 5·6 per cent. $C_{14}H_{19}O_3N$ requires C, 67·4; H, 7·6; N, 5·6 per cent.

Ethyl N-(β-3:4-*dimethoxphenethyl*) *Glutaramate* (V, R = $(CH_2)_3$)

A stirred solution of homoveratrylamine (β-3:4-dimethoxyphenethylamine) (18·1 g.) in dry ether (150 ml.), cooled in ice-salt mixture was treated dropwise with a solution of γ-carbethoxybutyryl chloride (8·9 g., 0·5 equiv.) in dry ether (50 ml.), over a period of one hour. The stirring

was continued for a further two hours, the mixture left overnight, and then refluxed for a further two hours. Water (100 ml.) was added, and the product worked up as described by Battersby, Openshaw and Wood for ethyl *N*-(3:4-dimethoxyphenethyl) malonamate. Yield 12·9 g. (80 per cent). Recrystallised from dry ether with cooling in acetone and CO_2 to give fine, colourless needles (18·8 g.) m.p. 47–48°. Found: C, 63·5; H, 7·7; N, 4·4 per cent. $C_{17}H_{25}O_5N$ requires C, 63·1; H, 7·8; N, 4·3 per cent.

N-(*β*-3:4-*Dimethoxyphenethyl*) *Glutarimide* (X, R = $(CH_2)_3$)

Ethyl *N*-(3:4-dimethoxyphenethyl) glutaramate (1·61 g.) was added to a melted mixture of potassium hydrogen sulphate (5 g.) and anhydrous sodium sulphate (2 g.) and the mixture heated at 230–240° (bath temperature) for 45 minutes. The cooled mass was extracted with hot water, and after cooling the deposited imide was collected after skimming off a black tar from the surface of the solution. Yield 0·48 g. (35 per cent). Recrystallised from benzene and light petroleum (40 to 60°) as white needles, m.p. 113 to 114°. Found: C, 64·5; H, 6·8; N, 5·1 per cent. $C_{15}H_{19}O_4N$ requires C, 64·9; H, 6·9; N, 5·1 per cent.

Ethyl N-(*β*-3:4-*dimethoxyphenethyl*) *Adipamate* (V, R = $(CH_2)_4$)

This was prepared as described above for ethyl *N*-(3:4-dimethoxyphenethyl) glutaramate, using δ-carbethoxyvaleryl chloride (9·6 g.) prepared by the method of Blaise and Koehler[13]. Yield of adipamate 11·2 g. (69 per cent) as colourless needles, m.p. 46 to 47, 5° on crystallisation from ether. Found: C, 64·3; H, 8·3; N, 4·2 per cent. $C_{18}H_{27}O_5N$ requires C, 64·1; H, 8·1; N, 4·2 per cent.

Methyl N-(*β*-3:4-*dimethoxyphenethyl*) *Succinamate*

This was prepared in the same way as ethyl *N*-(3:4-dimethoxyphenethyl) glutaramate, using 36·2 g. of homoveratrylamine and *β*-carbmethoxypropionyl chloride (15·05 g., 0·5 equiv.), prepared by the method of Cason[14]. Yield 25 g. (85 per cent) yielding colourless needles, m.p. 66 to 67·5°, from benzene and light petroleum (40 to 60°). Found: C, 61·5; H, 7·1; N, 4·6 per cent. $C_{15}H_{21}O_5N$ requires C, 61·0; H, 7·1; N, 4·7 per cent.

N-(*β*-3:4-*Dimethoxyphenethyl*) *Succinimide*

Methyl *N*-(3:4-dimethoxyphenethyl) succinamate (2 g.) was heated at 230 to 240° with a mixture of potassium hydrogen sulphate (8 g.) and anhydrous sodium sulphate (2 g.) as described for *N*-*β*-(3:4-dimethoxyphenethyl) glutarimide. Yield 0·4 g. (22 per cent). Crystallised from alcohol in colourless needles m.p. 128-129°. Found: C, 63·6; H, 6·3; N, 5·3; MeO, 23·6 per cent. $C_{14}H_{17}O_4N$ requires C, 63·8; H, 6·5; N, 5·3; MeO, 23·6 per cent.

γ-Carbethoxy-β-iso*propylbutyryl Chloride*

γ-Carbethoxy-*β-iso*propylbutyric acid (5·05 g.) was heated with freshly-distilled thionyl chloride (11·9 g.) at 50 to 60° for 3½ hours. After the

excess of thionyl chloride had been removed *in vacuo* with the aid of dry benzene, the residue was distilled. Yield 7·1 g. (68 per cent) of colourless liquid, b.p. 75 to 76°/0·05 mm.

Ethyl N-(*β*-3:4-*dimethoxyphenethyl*)-*β*-iso*propyl Glutaramate* (V, R = $CH_2.CH(isoPr)CH_2$)

This was prepared from homoveratrylamine (12·5 g.) and *γ*-carbethoxy-*β*-*iso*propylbutyrylchloride (7·4 g., 0·5 equiv.) as described for ethyl *N*-(3:4-dimethoxyphenethyl) glutaramate. Yield 7·4 g. (60 per cent) of pale yellow gum, b.p. 275 to 280°/0·0005 mm. (decomp.). The product was purified by passing in a solution in benzene (dry) (0·3 g. in 25 ml.) through columns of activated alumina (2 × 10 cm.), developing with dry benzene (150 ml.) and eluting with ethanol benzene (1:20, 1400 ml.). Removal of the solvent from the eluate under reduced pressure yielded a colourless gum (0·252 g.). Found: C, 64·9; H, 8·4; N, 3·6 per cent. $C_{20}H_{31}O_5N$ requires C, 65·7; H, 8·6; N, 3·8 per cent.

NN-*Bis*(*β*-3:4-*dimethoxyphenethyl*) *Glutaramide* (VII, R = $(CH_2)_3$)

(*a*) Ethyl *N*-(*β*-3:4-dimethoxyphenethyl) glutaramate (3·23 g.) was heated with veratrylamine (1·81 g.) for 4 hours at 170 to 180° (oil bath). On cooling, a white solid mass, 2·9 g. (63 per cent) was obtained, which gave white needles, m.p. 130 to 131° from ethanol. The yield was increased to 73 per cent on repeating the experiment in a sealed tube (Carius furnace). Found: C, 65, 4; H, 7·6; N, 6·2 per cent. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·5; N, 6·1 per cent.

(*b*) The same compound was prepared from homoveratrylamine (3·62 g.) and diethyl glutarate (1·9 g.) by following Child and Pyman's method[9]. Yield 2·6 g. (75 per cent), m.p. 130 to 131°. Mixed m.p. with previous sample, 129 to 130° with softening at 127°.

NN-*Bis*-(*β*-3:4-*dimethoxyphenethyl*) *Adipamide* (VI, R = $(CH_2)_4$)

(*a*) From ethyl *N*-(3:4-dimethoxyphenethyl) adipamate (3·3 g.) and homoveratrylamine (1·81 g.) by heating at 190° to 200° as described above. Yield 2·8 g. (60 per cent) raised to 65 per cent in a sealed tube (Carius furnace), m.p. 169 to 170°.

(*b*) By Child and Pyman's method (see above) by heating homoveratrylamine (3·6 g.) and diethyl adipate (1·9 g.) at 190 to 200° for four hours. Yield 2·45 g. (74 per cent) m.p. 169 to 170°. Found: C, 66·2; H, 7·7; N, 5·9 per cent. $C_{26}H_{36}O_6N_2$ requires C, 66·1; H, 7·7; N, 5·9 per cent. Mixed m.p. with product (*a*), 169 to 170°.

NN-*Bis*(*β*·3:4-*dimethoxyphenethyl*) *Succinamide*

(*a*) From ethyl *N*-(3:4-dimethoxyphenethyl) succinamate (2·95 g.) and homoveratrylamine (1·81 g.) by heating for 4 hours at 170 to 180° (oil bath) as described above for the corresponding adipamide and glutaramide. Yield 2·35 g. (53 per cent) raised to 60 per cent when heating was conducted in a sealed tube. Colourless needles from benzene and light petroleum. m.p. 173 to 174°.

(*b*) By Child and Pyman's method, used above, by heating homoveratrylamine (8·6 g.) and diethyl succinate (4·1 g.) for four hours at 170 to 180°. The crude product (6·5 g.) was separated by boiling water into an insoluble portion (3·9 g., m.p. 168 to 170°) and a soluble fraction (2·2 g., m.p. 124 to 128°). The former yielded *NN*-bis-(β-3 : 4-dimethoxyphenethyl) succinamide, m.p. 173 to 174° from benzene and petroleum and the latter, after removal of the water under reduced pressure, gave *N*-(β-3 : 4-dimethoxyphenethyl) succinimide, m.p. 128 to 129° after repeated recrystallisation from ethanol. The melting points of both diamide and imide were undepressed when admixed with authentic samples. Found: C, 64·6; H, 7·5; N, 6·3 per cent. $C_{24}H_{32}O_6N_2$ requires C, 64·8; H, 7·3; N, 6·3 per cent.

NN-*Bis*-(β-3 : 4-*dimethoxyphenethyl*)β-*methyl Glutaramide* (VI, R = $CH_2CH(CH_3)CH_2$)

Diethyl β-methyl glutarate (10·1 g.) and homoveratrylamine (18·1 g.) were heated for 4 hours at 200 to 210° (flask fitted with condenser). After cooling, benzene (50 ml.) was added and the whole set aside for 17 hours. The solid (9 g.) was washed with cold ethanol. A second crop (1·5 g.) was obtained by concentrating the benzene and ethanol mother liquors. Total yield 10·5 g. (45 per cent). Needles, m.p. 157 to 158°, from ethanol. Found: C, 65·8; H, 7·6; N, 5·9 per cent. $C_{26}H_{36}O_6N_2$ requires C, 66·1; H, 7·7; N, 5·9 per cent.

The mother liquors from this experiment (and two other batches) were evaporated to quarter bulk and left in a refrigerator for one week. The crystals (3·1 g.) which had separated yielded small needles, m.p. 119 to 120° after four recrystallisations from ethanol. This compound was shown to be N-(β-3 : 4-*dimethoxyphenethyl*)β-*methyl glutarimide* (see below). Mixed m.p. with authentic sample 118 to 120°. Found: C, 65·4; H, 7·0; N, 5·1 per cent. $C_{16}H_{21}O_4N$ requires: C, 65·9; H, 7·2; N, 4·8 per cent.

NN-*Bis*(β-3 : 4-*dimethoxyphenethyl*) β-iso*Propyl Glutaramide* (VI, R = $CH_2.CH(iso\text{Pr})–CH_2$)

(*a*) Homoveratrylamine (18·1 g.) and diethyl β-*iso*propylglutarate (11·5 g.) were heated at 190 to 200° for 4 hours, and the product worked up as described above for the corresponding β-methylglutaramide. Yield 8 g. (33 per cent). Small needles, m.p. 156 to 157°, from ethanol. Found: C, 67·2; H, 7·8; N, 5·5 per cent. $C_{28}H_{40}O_6N_2$ requires C, 67·2; H, 8·1; N, 5·6 per cent.

The mother liquors, on concentrating to quarter bulk and leaving in the refrigerator for three days yielded N-(β-3 : 4-*dimethoxyphenethyl*) β-iso*propyl glutarimide*; 2·6 g. (17 per cent), m.p. (after four recrystallisations from aqueous ethanol) 119 to 120°. Found: C, 67·7; H, 7·9; N, 4·4 per cent. $C_{18}H_{25}O_4N$ requires C, 67·9; H, 7·9; 4·4 per cent.

(*b*) Ethyl*N*-(β-3 : 4-dimethoxyphenethyl)β-*iso*propyl glutaramate (3·6 g.) and homoveratrylamine (1·8 g.) were heated together at 190 to 200° for 4 hours. The solid obtained on cooling, 2·1 g. (42 per cent) yielded, on recrystallisation from ethanol, small needles, m.p. 156 to 157°, undepressed when admixed with a sample obtained by method (a).

1 : 3-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*) *propane* (VII, R = $(CH_2)_3$) (see Osbond[8]).

To a solution of *NN*-(β-3 : 4-dimethoxyphenethyl) glutaramide (2·29 g.) in anhydrous boiling toluene (30 ml.), phosphorus pentoxide (7 g.) was added all at once with continuous stirring. More phosphorus pentoxide (7 g.) was added after half an hour. After refluxing for a total of three hours the product was cooled and the supernatant liquid decanted. The residue was decomposed with water and after extraction with ether (2 × 20 ml.) the aqueous solution was cautiously basified with ammonium hydroxide solution. The yellow oil which separated was extracted with ether (5 × 50 ml.) and the ethereal solution dried and evaporated. The crude product was crystallised from ethanol. Yield 1·14 g. (54 per cent) of white felted needles, m.p., 161 to 163° (Osbond quotes 159 to 161°). Found: C, 70·8; H, 7·1; N, 6·5 per cent. $C_{25}H_{30}O_4N_2$ requires C, 71·1; H, 7·2; N, 6·6 per cent. Titration equivalent, 204; $C_{25}H_{30}O_4N_2$ requires 211. pKa = 6·8 (approx.).

1 : 4-*Bis*-(β-3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*) *butane* (VII, R = $(CH_2)_4$)

(*a*) This compound was obtained in the same way as the corresponding propane homologue using *NN*-bis-(β-3 : 4-dimethoxyphenethyl) adipamide (2·36 g.) in anhydrous toluene (35 ml.) and phosphorus pentoxide (2 × 8 g.). The crude product, 1·6 g. (72 per cent) crystallised from dry ethyl acetate in hard needles, m.p. 172 to 173°. Found: C, 72·2; H, 7·5; N, 6·0 per cent. $C_{26}H_{32}O_4N_2$ requires C, 71·5; H, 7·4; N, 6·4 per cent. Titration equivalent 216, $C_{26}H_{32}O_4H_2$ requires 218. pKa = 7·5 (approx.).

(*b*) *Using phosphorus oxychloride.* *NN*-Bis-(β-3 : 4-dimethoxyphenethyl) adipamide (2·36 g.), dry toluene (30 ml.) and freshly-distilled phosphorus oxychloride (7 ml.) were refluxed for one hour. After cooling, and decanting the toluene, the residue was washed with light petroleum (40 to 60°), dried and dissolved in ethanol (50 ml.), and basified with solution of sodium hydroxide. The free base was precipitated on the addition of water. Yield 1·8 g. (82 per cent).

1 : 3-*Bis*-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)β-*methyl propane* (VII, R = *iso*Pr)

This was obtained in the same way as the corresponding *n*-propane homologue, using *NN*-bis-(β-3 : 4-dimethoxyphenethyl)-β-methylglutaramide (4·72 g.), dry toluene (100 ml.) and phosphorus pentoxide (2 × 15 g.) at a bath temperature of 110 to 120°. Yield 3·0 g. (69 per cent). Crystals from ethyl acetate, m.p. 172 to 173°. Found: C, 71·0; H, 7·5; N, 6·1 per cent. $C_{26}H_{32}O_4N_2$ requires C, 71·5; H, 7·4; N, 6·4 per cent. Titration equivalent 213. $C_{26}H_{32}O_4N_2$ requires 218. pKa = 6·8 (approx.).

Dipicrate m.p. 172 to 173·5° after drying for 4 hours at 100° over P_2O_5 *in vacuo*. Found: C, 57·2; H, 4·3; N, 12·8 per cent. $C_{38}H_{38}O_{18}N_8$ requires C, 57·0; H, 4·3; N, 12·5 per cent.

Dihydrochloride from hydrochloric acid gas and the base in dry benzene. Recrystallised from methanol and ether m.p. 175 to 177° (decomp.).

Found: C, 58·0; H, 6·6; N, 5·2; Cl, 14·0 per cent. $C_{26}H_{34}O_4N_2Cl_2$ requires C, 61·5; H, 6·7; N, 5·5; Cl, 13·9 per cent.

Dimethiodide m.p. 190 to 192° dried over P_2O_5 *in vacuo* at 100°. Found: C, 45·1; H, 5·4; N, 3·7; I, 36·0 per cent. $C_{28}H_{38}O_4N_2I_2$ requires C, 46·6; H, 5·3; N, 3·8; I, 35·2 per cent.

Chlorplatinate Found: Pt, 24·0 per cent. $C_{26}H_{34}O_4N_2PtCl_6$ requires Pt, 23·0 per cent.

1 : 3-*Bis*(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-iso*propylpropane* (VII R = $-CH_2{\cdot}CH(isoPr)CH_2-$)

This was obtained in the same way as the corresponding *n*-propane homologue, using *NN*-bis-(β-3 : 4-dimethoxyphenethyl)-β-*iso*propylglutaramide (5 g.) dry toluene (50 ml.) and phosphorus pentoxide (2 × 15 g.) at a bath temperature of 110 to 115°. Yield 3·6 g. of brown gum which was finally crystallised from ether/light petroleum (40 to 60°) (charcoal). Repeated crystallisations gave colourless prisms m.p. 78 to 80°. Found C, 70·0; H, 7·9; N, 5·6 per cent. $C_{28}H_{36}O_4N_2$ requires C, 72·4; H, 7·8; N, 6·0 per cent. Better analytical results could not be obtained and the ultra-violet light absorption spectrum did not conform with those of homologous compounds. (On repeating the above experiment at a temperature of 120 to 130° for four hours the only isolable product proved to be *N*-(β-3 : 4-dimethoxyphenethyl)-β-*iso*propylglutarimide, m.p. 119 to 120° (see above). Mixed m.p. with authentic sample 118 to 120°).

Dipicrate. The substance of m.p. 78 to 80° yielded after repeated recrystallisations a dipicrate, m.p. 194·5 to 196°. Found C, 52·6; H, 4·5; N, 12·0 per cent. $C_{40}H_{42}O_{18}N_8$ requires C, 52·1; H, 4·6; N, 12·1 per cent.

Dimethiodide, *dihydrochloride*, and *platinichloride* of the base were all obtained but none yielded satisfactory analytical results.

Ethyl-γ-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso-*quinolyl*) *Butyrate* (XI, R = $(CH_2)_3$)

Ethyl *N*-(β-3 : 4-dimethoxyphenethyl) glutaramate (3·23 g.) anhydrous toluene (35 ml.) and freshly-distilled phosphorus oxychloride (10 ml.) were heated at 120 to 130° (oil bath) for 45 minutes. After cooling the mixture was diluted with light petroleum (40 to 60°, *c.* 50 ml.). After 2 hours the solvent was decanted and the brown gum dissolved in water (30 ml.) by slightly warming. After the removal of non-basic matter with ether (2 × 10 ml.) the aqueous solution was basified with dilute solution of ammonia and extracted with ether (5 × 20 ml.) and ethyl acetate (2 × 15 ml.) and the combined extracts dried over sodium sulphate (anhydrous). On evaporation of the solvent 2·3 g. (75 per cent) of yellow gum was obtained. This yielded long buff-coloured prisms from petroleum (80 to 100°). Found: C, 66·8; H, 7·6; N, 4·6 per cent $C_{17}H_{23}O_4N$ requires C, 66·9; H, 7·6; N, 4·6 per cent. Titration equivalent 301, pKa 7·4 (approx.) $C_{17}H_{23}O_4N$ requires 305. *Picrate*, m.p. 172 to 173·5°. Found: C, 51·9; H, 5·2; N, 10·7 per cent. $C_{23}H_{26}O_{11}N_4$ requires C, 51·7; H, 4·9; N, 10·5 per cent. *Hydrochloride*, m.p. 124 to

125°. Found: C, 59·6: H, 6·9; N, 4·0; Cl, 10·1 per cent. $C_{27}H_{24}O_4NCl$ requires C, 59·9; H, 7·1; N, 4·1; Cl, 10·4 per cent.

1 : 3-*Bis*-(6 : 7-*dimethoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-iso*quinolyl*) *propane* (VIII, R = $(CH_2)_3$)

The corresponding dihydro compound (1 g.) dissolved in glacial acetic acid (15 ml.) was treated with Adams' platinum catalyst (0·05 g.) and hydrogenated at room temperature and pressure. Uptake of hydrogen after 2 hours 118 ml.; theory requires 106 ml. After filtration, the solvent was removed *in vacuo*. The residual oil (1 g.) failed to crystallise (*cf.* Osbond[7]).

Dipicrate from ethanol (72 per cent of theory). Yellow needles, m.p. 211 to 213° (decomp.). Found: C, 49·9; H, 4·9; N, 10·4 per cent. $C_{37}H_{40}O_{18}N_8$ requires C, 50·2; H, 4·6; N, 12·6 per cent.

Dihydrochloride, needles from methanol, m.p. 265 to 268° (decomp.). Equivalent weight (by titration) 251; $C_{25}H_{36}O_4N_2Cl_2$ requires 249. pKa = 8·2 (approx.).

1 : 4-*Bis*(6 : 7-*dimethoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-iso*quinolyl*) *butane* (VIII, R = $(CH_2)_4$)

The corresponding bis dihydro compound (1 g.) in methanol (25 ml.) with Adams' catalyst (0·075 g.) was hydrogenated as described for the corresponding propane. Uptake of hydrogen after 2½ hours = 112 ml.; theory requires 103 ml. The oil remaining after the removal of solvent finally yielded needles m.p. 127 to 128° from ethyl acetate. (Child and Pyman[9] quote 126 to 127°). Found: C, 70·4; H, 8·1; N, 6·3 per cent. $C_{26}H_{36}O_4N_2$ requires C, 70·9; H, 8·2; N, 6·4 per cent.

1 : 3-*Bis*(3 : 4-*dimethoxy*-1 : 2 : 3 : 4 : *tetrahydro*-1-iso*quinolyl*)β-*methylpropane Dihydrochloride* (VIII, R = *iso*Pr)

This was prepared in the same way, and using the same quantities for 1 : 3-bis-(6 : 7-dimethoxy-1 : 2 : 3 : 4 : tetrahydro-1-*iso*quinolyl) propane. Uptake of hydrogen after 3 hours 115 ml.; theory requires 103 ml. The residual oil failed to crystallise after removal of the acetic acid. It was taken up in dry benzene and converted into the hydrochloride. Yield after three recrystallisations from methanol and ether 0·6 g., 50 per cent of theory. m.p. 278 to 280° (decomp.). Found: C, 59·7; H, 7·2; N, 5·1; Cl, 14·2 per cent. $C_{26}H_{38}O_4N_2Cl_2$ requires C, 60·8; H, 7·5; N, 5·4; Cl, 13·8 per cent. Equivalent weight by titration = 249. Theory requires 256·7. pKa = 8·2 approx..

1 : 3-*Bis*(3 : 4-*dimethoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-iso*quinolyl*)β-*methylpropane Dihydrobromide*

This was prepared from the corresponding bisdihydro-β-methylpropane using tin and hydrochloric acid as described by Osbond[7] for the *n*-propane derivative. Yield of dihydrobromide, 0·78 g., from 1 g. of bisdihydro-compound. Prisms from ether and methanol m.p. 276 to 278° (decomp.). Found: C, 49·9; H, 6·2; N, 4·5; Br, 26·3 per cent. $C_{26}H_{38}O_4H_2Br_2$ requires C, 51·8; H, 6·3; N, 4·7; Br, 26·5 per cent.

Measurement of Ultra-violet Absorption Spectra

Solutions contained about 2 mg. accurately weighed, in 100 ml. of 0·1N HCl. Absorption was measured between the wavelengths of 220 and 330 mμ in 1 cm. cells with a Hilger Uvispek and a hydrogen arc.

Calculation of the approximate pKa Values

A suitable quantity of free base or hydrochloride was dissolved in 100 ml. of a mixture of 3 parts of ethanol, 97 per cent, and 2 parts of distilled water and titrated potentiometrically with 0·1 N HCl, or 0·1 N NaOH. A Morton D.C. amplifier pH meter was employed, with glass and saturated calomel electrodes. The approximate pKa values were calculated from measurements of the pH of the solutions at half neutralisations.

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