934. *Chemical Constitution and Amoebicidal Action. Part II.* Synthesis of 2-(1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl-1-isoquinolylmethyl)-1-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-isoquinolyl)-butane and -pentane and Other Analogues of Emetine.*

By J. M. Osbond.

With a Biological Note.

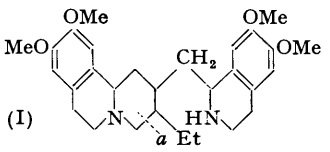
By J. D. Fulton and D. F. Spooner.

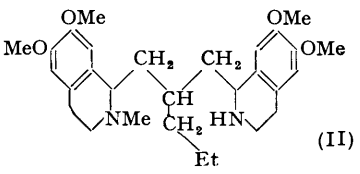
Analogues of emetine (I) have been prepared and include certain bistetrahydro*iso*quinolylalkanes (VII; R = alkyl, R′ = R″ = H or Me), the chief aim being the synthesis of the compound (II) derived from the emetine formula (I) by bond fission at *a*. These compounds (VII) were prepared from the appropriate *NN′*-diarylethyl glutardiamides (III; R = Et or Pr) by double ring closure to give the bisdihydro*iso*quinolylalkanes (IV; R = Et and Pr) which gave mono- (VI) and di-quaternary methiodides (VIII). These three pairs were then catalytically reduced. None of the compounds prepared, however, was active in concentrations up to 1 : 10^4 *in vitro* against *E. histolytica*, whereas emetine under similar conditions was active at 1 : 10^6. As a development of this work ethyl β-2-phenoxyethylglutarate was prepared for a projected synthesis of racemic " bisnoremetine."

Previous syntheses of analogues of emetine (I) have not resulted in compounds of comparable activity (Child and Pyman, *J.*, 1929, 2010; *J.*, 1931, 36; Part I *), although certain bisalkylaminoalkanes, which may be regarded as being formally derived from emetine, were more active *in vitro* (Pyman, *J. Soc. Chem. Ind.*, 1937, **56**, 789; Goodson, Goodwin, Gorvin, Goss, Kirby, Lock, Neal, Sharp, and Solomon, *Brit. J. Pharmacol.*, 1948, **3**, 49; Hall, Mahboob, and Turner, *J.*, 1952, 1956); and slight modifications of the emetine structure, as represented by the minor alkaloids of the ipecacuanha group, result in loss or diminution of activity against *E. histolytica* (Dobell and Laidlaw,

* Part I, *J.*, 1951, 3464.

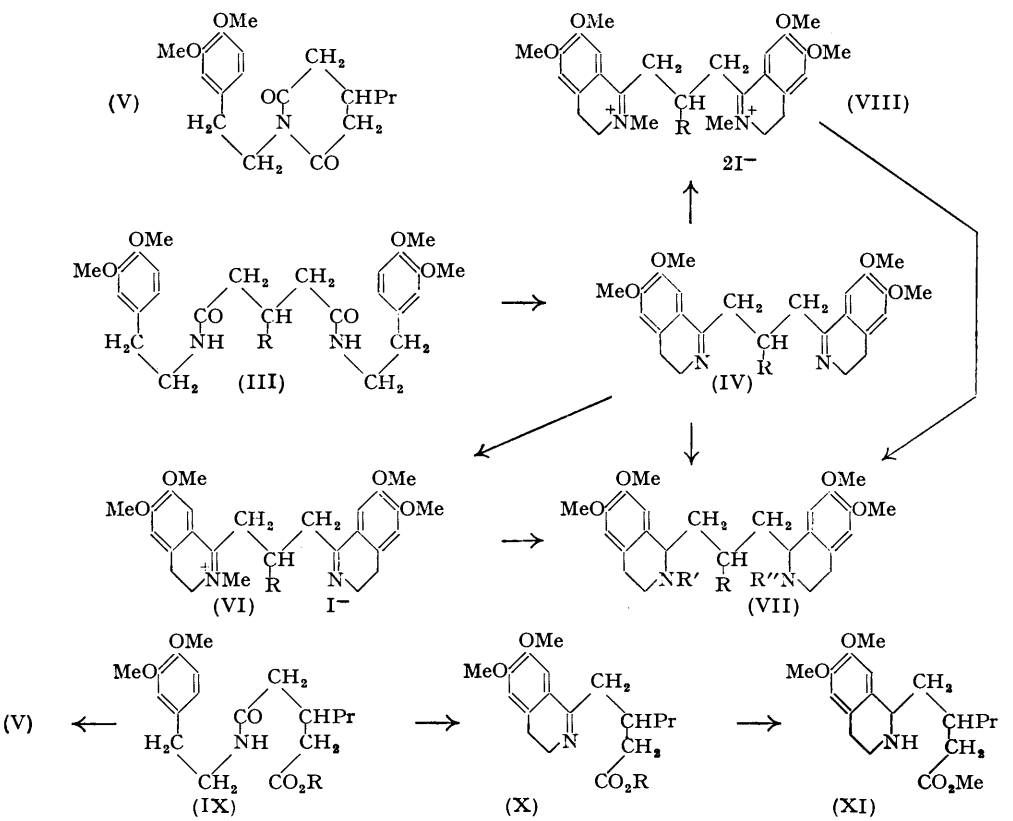
Parasit., 1926, **18**, 206; Jepps and Meakins, *Brit. Med. J.*, 1917, II, 645; Wenyon and O'Connor, *J. Roy. Army Med. Corps*, 1917, **28**, 473). However, although emetine in its biological action appears to be highly specific, it was considered worth while to prepare certain bistetrahydro-1-*iso*quinolylalkanes, in particular (II), which are derived from the





emetine formula (I) by fission of the C–C bond at *a* and thus possess the two basic groups, one secondary and one tertiary, separated by five carbon atoms as in emetine. Another aim of the present work was to discover if the methods of synthesis described below were general and could be adapted to a synthesis of the emetine nucleus.

In Part I,* two methods were described for the synthesis of 1 : 3-bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane (IV; R = H). The first involved the condensation of formaldehyde with two molecules of ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylacetate followed by hydrolysis and decarboxylation of the carbethoxy-groups, and the second involved the dicyclisation of the glutardiamide (III; R = H) with phosphoric oxide



in toluene. On reduction, (IV; R = H) gave the two racemates (VII; R = R′ = R″ = H) neither of which possessed appreciable activity against *E. histolytica in vitro*. It was hoped that both these methods could be employed in the synthesis of (IV; R = Et or Pr). In attempts to condense ethyl 3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl-

acetate with propaldehyde or butyraldehyde in the presence of sodium ethoxide or hydrogen chloride at room temperature only starting material was recovered and when the condensation was carried out in dilute acetic acid solution (cf. Part I) no crystalline product was obtained. The alternative method, dicyclisation of (III), was however satisfactory.

β-Propylglutaric acid was conveniently obtained by condensing butyraldehyde with two molecules of cyanoacetamide and then hydrolysing and decarboxylating the αα′-dicyano-β-propylglutaramide with concentrated hydrochloric acid (Day and Thorpe, *J.*, 1920, 1465). The ethyl ester and 2-(3 : 4-dimethoxyphenyl)ethylamine at 200° gave *NN′*-bis-2-(3 : 4-dimethoxyphenyl)ethyl-β-propylglutaramide (III; R = Pr), with a small amount of *N*-2-(3 : 4-dimethoxyphenyl)ethyl-β-propylglutarimide (V). The structure of (V) was proved by treating 2-(3 : 4-dimethoxyphenyl)ethylamine with β-propylglutaric anhydride in benzene and treating the product (IX; R = H), with acetic anhydride, which gave (V), or with phosphoric oxide in toluene which gave (V) together with (X; R = H). An attempt to dicyclise the methyl ester (IX; R = methyl) to a benzopyridocolone with phosphorus oxychloride in toluene yielded only (X; R = Me) (cf. Haworth, Perkin, and Pink, *J.*, 1925, 1709) which on catalytic reduction gave the tetrahydro*iso*quinoline (XI).

The glutardiamide (III; R = propyl) gave undesired products by side reactions on cyclisation by phosphorus oxychloride in toluene (cf. Child and Pyman, *loc. cit.*, 1929; Osbond, *loc. cit.*), but treatment with phosphoric oxide in toluene gave a 40% yield of (IV; R = Pr), characterised as the dihydrochloride and dihydrobromide. Reduction of this with tin and hydrochloric acid gave no useful result, but hydrogenation in presence of Adams's catalyst in dilute hydrochloric acid yielded, after rather tedious fractionation of the dihydrogen dioxalates, the two racemates (VII; R = Pr, R′ = R″ = H).

When the bisdihydro*iso*quinolylalkane (IV; R = Pr) was refluxed with an excess of methyl iodide, the dimethiodide (VIII; R = Pr) was formed, which on catalytic reduction gave the dihydriodide of the bistetrahydro-compound (VII; R = Pr, R′ = R″ = Me). Use of 1 mol. of methyl iodide in benzene at room temperature led to the monomethiodide (VI; R = Pr). This was somewhat unstable when recrystallised but it was possible to reduce the crude methiodide catalytically in methanol to the hydriodide of the monomethyl derivative (VII; R = propyl, R′ = Me, R″ = H), only one isomer being isolated.

For biological testing the next lower homologues were prepared similarly from ethyl β-ethylglutarate. Catalytic reduction of the bisdihydro*iso*quinolylalkane (IV; R = Et) was first carried out in dilute hydrochloric acid and after fractional crystallisation of the dihydrogen dioxalates two racemates (VII; R = Et, R′ = R″ = H) were isolated, but if reduction was carried out in methanol separation of the two isomers was easier and the yields were better.

It was thought that the general route (III) ⟶ (IV) ⟶ (VII) might be adapted to the synthesis of racemic " bisnoremetine " (I; without the ethyl group). If, for instance, the compound (IV; R = $CH_2{\cdot}CH_2{\cdot}OPh$) or (VII; R = $CH_2{\cdot}CH_2{\cdot}OPh$, R′ = R″ = H) could be obtained, replacement of the phenoxy-group by bromine would after cyclisation lead to the formation of the fifth ring of emetine. So ethyl β-2-phenoxyethylglutarate (XII) was synthesised as shown in the scheme. At this point Pailer and Strohmayer

$$PhO{\cdot}[CH_2]_3{\cdot}CH(CO_2H)_2 \longrightarrow PhO{\cdot}[CH_2]_3{\cdot}CBr(CO_2H_2) \xrightarrow[\text{steps}]{\text{Two}}$$

$$PhO{\cdot}[CH_2]_3{\cdot}CHBr{\cdot}CO_2Et \longrightarrow PhO{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}CO_2Et \longrightarrow PhO{\cdot}[CH_2]{\cdot}CH\begin{<}{CH_2{\cdot}CO_2Et \atop CH(CO_2Et)_2}\end{} \longrightarrow$$

$$PhO{\cdot}[CH_2]_2{\cdot}CH\begin{<}{CH_2{\cdot}CO_2H \atop CH(CO_2H)_2}\end{} \longrightarrow PhO{\cdot}[CH_2]_2{\cdot}CH(CH_2{\cdot}CO_2Et)_2 \quad (XII)$$

(*Monatsh.*, 1951, **82**, 1125) reported the synthesis of (XII) by the same route and for the same purpose. Where physical constants are given for their intermediates they agree with ours. As no experimental details have been given in their note we record our synthesis in the Experimental section.

Biological Note.—Apart possibly from monkeys there is no entirely suitable laboratory

animal to serve as host for the screening of potential amoebicides. For that reason *in vitro* tests, with all their inherent draw-backs, in which *E. histolytica* is cultured in presence of a mixed bacterial flora or with a single bacterial species, have been widely employed for the evaluation of new drugs. The preliminary results obtained in this way should be followed by animal or clinical tests after the necessary data on pharmacology and toxicology have been obtained. As *E. histolytica* can only be cultured in the presence of bacteria, it is essential that a lethal action by chemical agents on the amoebæ be distinguished from that on the accompanying bacteria which, if affected, would indirectly produce the same result. Such antibacterial action might, however, be a desirable additional property in any drug. Dobell and Neal (*Parasit.*, 1952, **42**, 16) were able to culture *E. histolytica* in the presence of a single bacterium and we have used the methods of test described by Dobell (*Ann. Soc. belg. Med. trop.*, Liber Jubilaris J. Rodhain, 1947, 201) as modified by Fulton, Joyner, King, Osbond, and Wright (*Proc. Roy. Soc.*, 1950, *B*, **137**, 356).

A strain of *E. histolytica* originally isolated from a human patient by Dobell and cultured in the presence of a single organism (a smooth non-motile form of *Bacillus coli communis*) was used. The culture medium was monophasic and consisted of inactivated horse serum 1 part, Ringer's solution 8 parts, and 0·2% of Na_2HPO_4 to give pH 7·2 with the addition of 20% of Wright's broth. Each l. of this medium was mixed with 10 ml. of sterile 0·1% methylene-blue solution, which is without action on the amoeba and serves as indicator, being reduced in presence of the actively growing *B. coli*. A pure culture of the latter was grown on a serum–agar slope and suspended in 2% glucose broth so that each ml. contained 30×10^8 organisms as determined by an opacity standard. One drop of this suspension readily reduced methylene-blue without overgrowth of bacteria after 24 hours at 37° and conditions were then regarded as suitable for the growth of *E. histolytica*. When reduction of methylene-blue was prevented through bactericidal action of a drug the test could not be used. Each drug under test was dissolved in the medium and added to the tubes containing methylene-blue so as to give the desired concentration, duplicate tubes being used for each dilution. In preliminary tests of any substance concentrations of $1 : 10^3$, $1 : 10^4$, and $1 : 10^5$ were first employed. Amoebæ contained in the sediment of other culture tubes were added, in 0·1 ml. portions, to 6 control tubes without drug and to those in which drug was present, generally 42 in number, representing seven drugs. Emetine was frequently included in the test with each batch of drugs. After 3 days' incubation the results were read by withdrawal of some sediment from the tube and examination of the fresh preparation under the microscope with a $\frac{1}{6}$" objective and 6× eyepiece. The end-point was taken as that dilution of drug in which no live amoebæ could be found. The result in cases of doubt was checked by subculture in fresh medium. The results are tabulated.

Inactive

(IV; R = Et)
(VII; R = Et, R′ = R″ = H; racemate A)
(VIII; R = Et or Pr)

Active at $1 : 10^3$

(VII; R = Et, R′ = R″ = H; racemate B)

Active at $1 : 10^6$

Emetine

Inactive at $1 : 10^4$

(IV; R = Pr)
(VII; R = Pr, R′ = Me, R″ = H or Me)
(VII; R = Et, R′ = Me, R″ = H)

Active at $1 : 10^4$

(VII; R = Pr, R′ = R″ = H; racemate A)
(VII; R = Et, R′ = R″ = Me)
(VII; R = Pr, R′ = R″ = H; racemate B)

Experimental

Ethyl β-Ethylglutarate (cf. Day and Thorpe, *loc. cit.*).—Freshly distilled propaldehyde (33 g.) was added to cyanoacetamide (96 g.) in water (720 c.c.). The solution was cooled to 15° and aqueous potassium hydroxide (1 c.c.; 50%) was added and after 1 hour at room temperature it was stored overnight at 0°. The precipitate (formed 0·5 hour after the addition of alkali) was filtered off, dried, and refluxed in concentrated hydrochloric acid (700 c.c.) and water (700 c.c.) for 5·5 hours by which time all the carbon dioxide had been evolved. The solution was saturated with sodium chloride and extracted with ether several times. The extracts were dried (Na_2SO_4) and gave, after removal of solvent, β-ethylglutaric acid as a gum which rapidly crystallised. The crude acid was esterified (ethyl alcohol–sulphuric acid; refluxing overnight) and the product on vacuum-distillation gave the *ethyl* ester (68 g.), b. p. 102—104°/0·5 mm. A portion, redistilled, had b. p. 117—117·5°/2·0 mm., n_D^{21} 1·4431 (Found : C, 61·2; H, 9·7. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·3%).

Ethyl β-Propylglutarate.—Butyraldehyde (18·02 g.) similarly gave the ester (28 g.), **b.** p. 110—115°/2 mm.

NN′-*Bis*-2-(3 : 4-*dimethoxyphenyl*)*ethyl*-β-*ethylglutardiamide* (III; R = Et).—Ethyl β-ethylglutarate (10·8 g.) and 2-(3 : 4-dimethoxyphenyl)ethylamine (18·1 g.) were heated in an open flask at 200—210° for 3·5 hours. The mixture was cooled and benzene (*ca.* 50 c.c.) was added. The solid (8·12 g.) was collected and recrystallised from alcohol from which the *amide* (5·7 g.) separated as needles, m. p. 155—157° (Found: C, 66·7; H, 7·7; N, 5·7. $C_{27}H_{38}O_6N_2$ requires C, 66·65; H, 7·9; N, 5·8%). The benzene mother-liquor from this experiment and another conducted on twice the scale were concentrated and cooled to −5°. The solid which slowly separated was collected and recrystallised twice from alcohol from which N-2-(3 : 4-*dimethoxyphenyl*)*ethyl*-β-*ethylglutarimide* (1·54 g.) separated as plates, m. p. 126—127° (Found: C, 67·0; H, 7·3; N, 4·55. $C_{17}H_{23}O_4N$ requires C, 66·9; H, 7·6; N, 4·6%).

NN′-*Bis*-2-(3 : 4-*dimethoxyphenyl*)*ethyl*-β-*propylglutardiamide* (III; R = Pr).—Ethyl β-propylglutarate (19 g.) and 2-(3 : 4-dimethoxyphenyl)ethylamine (28 g.) were heated at 200—215° for 4 hours as in the above experiment. On dilution with benzene a jelly-like solid separated which partly crystallised overnight. When carried out at 180° the reaction was incomplete. The *amide* (14 g.) separated from benzene as needles, m. p. 114° (Found: C, 67·1; H, 7·7. $C_{28}H_{40}O_6N_2$ requires C, 67·2; H, 8·05%). From the benzene mother-liquor on concentration a second compound separated from aqueous alcohol as square prisms (1·0 g.), m. p. and mixed m. p. with N-2-(3 : 4-*dimethoxyphenyl*)*ethyl*-β-*propylglutarimide* (see below) 100—101° (Found: C, 67·7; H, 7·8; N, 4·6. $C_{18}H_{25}O_4N$ requires C, 67·7; H, 7·9; N, 4·4%). From the mother-liquor, on vacuum-distillation 2-(3 : 4-dimethoxyphenyl)ethylamine (8 g.), b. p. 110°/0·75 mm., was obtained.

N-2-(3 : 4-*Dimethoxyphenyl*)*ethyl*-β-*propylglutaramic Acid* (IX; R = H).—β-Propylglutaric anhydride (7·8 g.; Day and Thorpe, *loc. cit.*) in benzene (25 c.c.) was added to 2-(3 : 4-dimethoxyphenyl)ethylamine (9·05 g.) and after the vigorous reaction had subsided the mixture was refluxed for 1 hour. The solution was cooled, light petroleum (b. p. 40—60°) was added, and a white solid precipitated on scratching. Recrystallisation from benzene afforded the *acid* as small flat prisms (15 g.), m. p. 82—83° (Found: C, 64·4; H, 7·8; N, 4·15. $C_{18}H_{27}O_5N$ requires C, 64·1; H, 8·1; N, 4·15%).

N-2-(3 : 4-*Dimethoxyphenyl*)*ethyl*-β-*propylglutarimide* (V).—(*a*) The glutaramic acid (3 g.) described above was heated in acetic anhydride (10 c.c.) on the water bath for 0·5 hour. After the excess of anhydride had been removed under reduced pressure, ethanol was added and then a few drops of water. The crystalline material (0·55 g.) separated from aqueous alcohol as square prisms, m. p. and mixed m. p. with the material described above, 100—101°.

(*b*) The glutaramic acid (3·37 g.) in boiling toluene (75 c.c.) was treated with phosphoric oxide (20 g.) and refluxed for 1·5 hours at/130° (oil-bath). The toluene was decanted off and the residue dissolved in water. After separation of more toluene and extraction once with ether, the aqueous solution was basified with aqueous sodium hydroxide (50%) and then extracted with ether, which, however, only contained a trace of material. The solution was then adjusted to pH 7 and extracted twice with chloroform which yielded a reddish gum. The gum gave, in ethanol, a picrate (0·3 g.) as tablets, m. p. 179—181°, and was considered to be 3-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*hexanoic acid picrate* (Found: C, 52·9; H, 5·2; N, 10·5. $C_{18}H_{25}O_4N,C_6H_3O_7N_3$ requires C, 52·55; H, 5·1; N, 10·2%). The combined toluene and ether extracts gave on evaporation to dryness a crystalline residue which on recrystallisation yielded prisms (0·8 g.) of *N*-2-(3 : 4-dimethoxyphenyl)ethyl-β-propylglutarimide, m. p. and mixed m. p. 98—100°. Treatment of this glutarimide under more vigorous conditions with phosphoric oxide in xylene gave unchanged starting material.

Methyl 3-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*hexanoate Hydrochloride* (cf. X; R = Me).—*N*-2-(3 : 4-Dimethoxyphenyl)ethyl-β-propylglutaramic acid (5 g.) in methanol (50 c.c.) was saturated at 0° with dry hydrogen chloride. After being kept overnight at room temperature the solution was diluted with water and extracted twice with ether. The ethereal extracts, after being washed with water and dilute sodium hydrogen carbonate solution and dried (K_2CO_3), yielded an oily methyl ester (3·5 g.). To a boiling solution of this in toluene (50 c.c.), phosphorus oxychloride (10 c.c.) was added and the solution refluxed for 1 hour. To the cooled yellow solution light petroleum (b. p. 40—60°) was added and the supernatant liquor was then decanted from the yellow oil which had separated. The oil was dissolved in water and made alkaline with 2N-sodium hydroxide. The basic material was extracted twice with ether and dried (K_2CO_3) and the resulting pale yellow mobile oil was converted into the *hydrochloride* by evaporation to dryness with a slight excess of dilute hydrochloric acid. The salt

separated from ethanol–ether as prisms (1·23 g.), m. p. 177—178° (on one occasion they melted at 160°, resolidified, and remelted at 178—179°) (Found : C, 61·6; H, 7·9; N, 4·0. $C_{19}H_{27}O_4N$,HCl requires C, 61·7; H, 7·5; N, 3·8%).

Methyl 3-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*hexanoate Hydrochloride* (cf. XI).—The dihydro*iso*quinolyl-ester hydrochloride (0·59 g.) described above was hydrogenated in methanol (15 c.c.) at room temperature and atmospheric pressure in the presence of Adams's catalyst (0·05 g.). The product, a crystalline solid (0·22 g.), m. p. 138—150°, gave after recrystallisation from ethanol–ether the *tetrahydroisoquinoline hydrochloride*, m. p. 150—152° (Found : C, 61·4; H, 8·5. $C_{19}H_{29}O_4N$,HCl requires C, 61·35; H, 8·1%).

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*isoquinolylmethyl*)*butane* (IV; R = Et).—To a solution of *NN'*-bis-2-(3 : 4-dimethoxyphenyl)ethyl-β-ethylglutardiamide (10·83 g.) in boiling dry toluene (200 c.c.) was added phosphoric oxide (30 g.), in one lot, with constant shaking to prevent the solid from caking, and after 0·5 hour a further quantity of phosphoric oxide (30 g.) was added. After refluxing for a total of 2·5 hours the mixture was cooled, the toluene decanted, and the resulting mixture decomposed with water with cooling. The toluene layer was separated and the aqueous extract, after one extraction with ether, was made alkaline by the slow addition of aqueous sodium hydroxide (50%). The yellow oil which separated solidified when scratched and cooled to 5°. The solid was dissolved in benzene and after filtration from a small amount of insoluble material the base separated on concentration as needles (5·22 g.), m. p. 140—142°. One further recrystallisation from benzene gave the pure *base* (4·3 g.), m. p. 149—150° (Found : C, 72·3; H, 7·6; N, 6·3. $C_{27}H_{34}O_4N_2$ requires C, 72·0; H, 7·6; N, 6·2%). The *dihydrobromide* separated from ethanol–ether as prisms, m. p. (air-dried sample) 168—170° (Found, on air-dried specimen : C, 47·7; H, 6·3; N, 4·4; H_2O, 10·3. $C_{27}H_{34}O_4N_2$,2HBr,4H_2O requires C, 47·4; H, 6·5; N, 4·1; H_2O, 10·6. Found, on specimen dried at 150°; C, 52·6; H, 6·6; N, 4·9. $C_{27}H_{34}O_4N_2$,2HBr requires C, 52·9; H, 5·9; N, 4·6%). The *dimethiodide* (VIII; R = Et) was prepared by refluxing the bisdihydro*iso*quinoline base (0·5 g.) with methyl iodide (5 c.c.) for 2 hours. The solid, which had separated rapidly, crystallised from methanol–ether as yellow prisms (0·65 g.), m. p. 175—176°. A portion, recrystallised from methanol, had, when air dried, m. p. 172—174° (Found, on air-dried specimen : C, 45·2; H, 6·0; N, 3·7; H_2O, 4·75. $C_{29}H_{40}O_4N_2I_2$,2H_2O requires C, 45·2; H, 5·75; N, 3·6; H_2O, 4·7. Found, on specimen dried at 150° *in vacuo* : C, 47·8; H, 5·8; N, 4·25. $C_{29}H_{40}O_4N_2I_2$ requires C, 47·4; H, 5·5; N, 3·8%).

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*pentane* (IV; R = Pr).—To a solution of *NN'*-2-(3 : 4-dimethoxyphenyl)ethyl-β-propylglutardiamide (7·5 g.) in boiling dry toluene (150 c.c.) phosphoric oxide (25 g.) was added with frequent shaking for the first 15 minutes, and then after 0·5 hour a further 25 g. of phosphoric oxide was added. After refluxing for a total of 2 hours the product was worked up as described above and crystallised from benzene as needles (2·2 g.), m. p. 123—125°, and a second crop (0·62 g.; m. p. 115—120°) was obtained on concentration. The *base* separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 125·5—126·5° (Found : C, 72·5; H, 7·9; N, 6·1. $C_{28}H_{36}O_4N_2$ requires C, 72·4; H, 7·8; N, 6·0%). No crystalline material could be obtained from the benzene mother-liquor but treatment with hydrochloric acid gave the *dihydrochloride* which separated from ethanol as yellow prisms (0·3 g.), m. p. 185—187° (decomp.) (Found, on air-dried specimen : C, 60·9, 60·8; H, 7·6, 7·3; N, 5·2. $C_{28}H_{36}O_4N_2$,2HCl,2H_2O requires C, 60·5; H, 7·3; N, 5·0. Found, on specimen dried at 150° *in vacuo* : Cl, 13·6; N, 5·6. $C_{28}H_{36}O_4N_2$,2HCl requires Cl, 13·2; N, 5·2%). The *dihydrobromide* separated from ethanol–ether in yellow prisms, m. p. 184—185° (decomp.) (Found, on air-dried specimen : C, 52·0; H, 6·2; N, 4·6; H_2O, 2·1. $C_{28}H_{36}O_4N_2$,2HBr,2H_2O requires C, 52·2; H, 6·25; N, 4·3; H_2O, 2·8%). The *dimethiodide* (VII; R = Pr), prepared by refluxing the base (0·3 g.) with methyl iodide (3 c.c.) for 2 hours, separated from methanol as yellow prisms (0·3 g.), m. p. 156—158° (decomp.) (Found, on air-dried specimen : C, 45·2; H, 5·8; N, 3·7; I, 31·8; H_2O, 4·85. $C_{30}H_{42}O_4N_2I_2$,2·5H_2O requires C, 45·4; H, 6·0; N, 3·5; I, 32·0; H_2O, 5·7. Found, on specimen dried at 120° : C, 47·9; H, 5·9; N, 4·2. $C_{30}H_{42}O_4N_2I_2$ requires C, 48·2; H, 5·65; N, 3·7%).

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*butane Dihydrogen Dioxalates* (cf. VII; R = Et, R' = R'' = H).—1-(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)butane (1·0 g.) was hydrogenated in methanol (30 c.c.) in the presence of Adams's catalyst (0·05 g.) at atmospheric pressure and room temperature. After 3 hours 135 c.c. of hydrogen had been taken up. The catalyst was removed and to the concentrated filtrate, oxalic acid (0·6 g.; hydrated) in methanol was added. On seeding and storage a solid slowly

separated. Two recrystallisations from methanol yielded the *dihydrogen dioxalate* (A) as cubic prisms (0·45 g.), m. p. 185—187° (Found: C, 58·95; H, 6·9; N, 4·9. $C_{27}H_{38}O_4N_2,2H_2C_2O_4$ requires C, 58·7; H, 6·7; N, 4·4%). The first methanol mother-liquor was concentrated and ether was added. After storage for some time and with the aid of a seed of the second isomer, a solid separated (0·32 g.) (m. p. 163—170°) which was not definitely crystalline. Recrystallisation from methanol–ether afforded needles of the *dihydrogen dioxalate* (B) which shrank at 176°, melted 177—179°, and gave a depression of m. p. to 172—178° on admixture with (A) (Found: C, 58·0; H, 7·0; N, 4·8%). In a previous reduction carried out in dilute hydrochloric acid the two isomers were separated by tedious fractional crystallisation as dihydrogen dioxalates and provided the seeds mentioned above. When crystallisation was from methanol, as recorded, the yields and separation of the two isomers were more satisfactory.

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*pentane Dihydrogen Dioxalates* (cf. VII; R = Pr, R′ = R″ = H).—1-(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)pentane (1·10 g.) in 3N-hydrochloric acid (5 c.c.) and water (15 c.c.) was hydrogenated as described above. After 3 hours the hydrogen uptake (140 c.c.) was complete; the catalyst was filtered off and the filtrate was made alkaline with 2N-sodium hydroxide, and the basic material was extracted twice with ether and dried (K_2CO_3). The gum (1·08 g.) thus obtained was added in ethanol to oxalic acid (0·6 g.) in ethanol and cooled to 0°. The white solid (0·49 g.) which was partly crystalline under polarised light gave after two recrystallisations from methanol the pure *dihydrogen dioxalate* (A) as needles, m. p. 181—183° (decomp.) (Found, on air-dried specimen: C, 55·7; H, 7·3; N, 4·4; H_2O, 5·3. $C_{28}H_{40}O_4N_2,2H_2C_2O_4,2H_2O$ requires C, 56·1; H, 7·1; N, 4·1; H_2O, 5·3. Found, on specimen dried at 120°: C, 58·75; H, 7·2; N, 4·4. $C_{28}H_{40}O_4N_2,2H_2C_2O_4$ requires C, 59·2; H, 6·8; N, 4·3%). The methanol mother-liquor on slow evaporation gradually deposited a white solid (0·25 g.), m. p. 193—194°, which afforded on recrystallisation from methanol the *dihydrogen dioxalate* (B), shrinking 196°, m. p. 200—202° (Found: C, 59·5; H, 7·1; N, 4·3%).

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolyl*)-2-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolylmethyl*)*butane Dihydrobromide* (cf. VII; R = Et, R′ = R″ = Me).—1-(3 : 4-Tetrahydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)butane dimethiodide (1·26 g.) in methanol (220 c.c.) was hydrogenated in the presence of Adams's catalyst (0·1 g.) at room temperature and atmospheric pressure. After the theoretical uptake of hydrogen (140 c.c.; 2·25 hours) the catalyst was removed, the filtrate concentrated, ether cautiously added, and the solution stored at 0°. The *dihydriodide* (0·54 g.), m. p. 240—241° (meniscus at 250°), separated as a microcrystalline solid (Found: N, 3·8. $C_{29}H_{42}O_4N_2,2HI$ requires N, 3·8%). A portion was dissolved in water and made alkaline, and the base was extracted with ether. The oil thus obtained yielded a *dihydrobromide* which separated from aqueous alcohol as a microcrystalline powder, m. p. 265—268° (decomp.) (Found: C, 53·7; H, 7·1; N, 4·7. $C_{29}H_{42}O_4N_2,2HBr$ requires C, 54·05; H, 6·9; N, 4·3%). When this catalytic reduction was carried out in dilute hydrochloric acid the solution became brown and no compound was characterised.

1-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolyl*)-2-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolylmethyl*)*pentane Dihydriodide* (cf. VII; R = Pr, R′ = R″ = Me).—1-(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)pentane dimethiodide (0·44 g.) in methanol (100 c.c.) was hydrogenated as described above. When ether was added to the filtrate prisms (0·18 g.) gradually separated. Recrystallisation from methanol afforded the *dihydriodide* as prisms, m. p. 235—237° (decomp.) (Found: C, 47·9; H, 6·5; N, 4·1. $C_{30}H_{44}O_4N_2,2HI$ requires C, 47·9; H, 6·2; N, 3·7%). The methanolic mother-liquor was concentrated but no more crystalline material was obtained, nor could a crystalline dihydrogen dioxalate be obtained from the residue.

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*butane Methiodide* (VI; R = Et).—Methyl iodide (0·56 g., 2 mols.) in dry benzene (4 c.c.) was added to a solution of 1-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)butane (0·9 g., 1 mol.) in benzene (20 c.c.) at room temperature and the whole kept overnight. The yellow *methiodide* precipitated (0·6 g.) was washed with ether and recrystallised from ethanol as small yellow prisms, m. p. 148—149° (Found: C, 56·4; H, 6·5; N, 4·8. $C_{28}H_{37}O_4N_2I$ requires C, 56·75; H, 6·3; N, 4·7%).

2-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolylmethyl*)-1-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*butane Hydriodide* (cf. VII; R = Et, R′ = Me, R″ = H).—The above monoquaternary salt (0·3 g.) was hydrogenated in methanol (50 c.c.) and at room

temperature and atmospheric pressure in the presence of Adams's catalyst. When absorption was complete the catalyst was removed and the filtrate concentrated and treated with a few drops of ether. The *hydriodide* separated as yellow prisms, m. p. 212—214° (Found : C, 55·4; H, 6·3; N, 4·7. $C_{28}H_{38}O_4N_2,HI,0{\cdot}5H_2O$ requires C, 55·7; H, 6·7; N, 4·6%).

1-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)-2-(3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)*pentane Methiodide* (VI; R = Pr).—Methyl iodide (0·14 g., 1 mol.) in benzene (5 c.c.) was added to 1-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*-quinolylmethyl)pentane (0·46 g., 1 mol.) in benzene (20 c.c.) at room temperature and stored in the dark. After 3 hours the solution became cloudy and next morning a pale yellow crystalline material together with some gum, which solidified on scratching, separated. This material (0·23 g.), m. p. 137—140°, was filtered off, washed with benzene, and dried, and could be used directly without further purification for reduction. Although this monoquaternary *methiodide* was somewhat unstable on recrystallisation from ethanol, it separated from methanol–ether as yellow prisms, m. p. 147—148° (Found : C, 57·0; H, 6·6; N, 4·8; I, 21·1. $C_{29}H_{39}O_4N_2I$ requires C, 57·4; H, 6·5; N, 4·6; I, 20·9%).

2-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolylmethyl*)-1-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*pentane Hydriodide* (cf. VII; R = Pr, R′ = Me, R″ = H).—The quaternary methiodide (0·23 g.) was hydrogenated in methanol (50 c.c.) at room temperature and as above (1 hour). The catalyst was removed and the filtrate concentrated. A powder (0·05 g.) slowly separated (m. p. 210°), which, when crystallised from methanol–ether, afforded prisms of the *hydriodide*, m. p. 215—216° (Found : C, 57·2; H, 7·2; N, 4·8. $C_{29}H_{42}O_4N_2,HI$ requires C, 57·05; H, 7·1; N, 4·6%).

α-*Bromo*-α-3-*phenoxypropylmalonic Acid*.—To α-3-phenoxypropylmalonic acid (71·4 g.) in ether (300 c.c.), bromine (15·9 c.c.) was added dropwise with stirring during an hour with water cooling; absorption was rapid. The ethereal solution was washed with water, dried, (Na_2SO_4), and evaporated to yield a yellow viscous oil. The oil was dissolved in chloroform, light petroleum (b. p. 40—60°) was added just to turbidity, and the solution then cooled to 0°. The crystals which separated (52 g.) were recrystallised from chloroform and light petroleum (b. p. 40—60°) and then several times from chloroform alone. The m. p. of the *bromomalonic acid* which formed plates was not sharp (49—52°), despite repeated recrystallisation from chloroform, but was finally raised to m. p. 55—60° but the acid was probably not completely homogeneous (Found : Br, 25·0. $C_{12}H_{13}O_5Br$ requires Br, 25·2%).

Ethyl 2-*Bromo*-5-*phenoxypentanoate*.—The bromomalonic acid (50 g.) was heated at 160—170° until gassing had ceased (0·5 hour). As attempts to obtain the free acid crystalline were unsuccessful, it was converted into the ethyl ester by boiling ethanol (500 c.c.) and concentrated sulphuric acid (2 c.c.) overnight. *Ethyl* 2-*bromo*-5-*phenoxypentanoate* (20 g.) had b. p. 146—148°/1·0 mm., m. p. 42—44° (from chloroform), n_D^{20} 1·5240 (Found : C, 52·1; H, 5·95; Br, 27·0. $C_{13}H_{17}O_3Br$ requires C, 51·85; H, 5·7; Br, 26·6%). Pailer and Strohmeyer, *loc. cit.*, give m. p. 40—41°.

Ethyl 5-*Phenoxypent*-2-*enoate*.—The bromo-ester (14·34 g.) was heated in diethylaniline at 160—180° for 10 hours. The dark solution was poured into excess of 3N-hydrochloric acid and then extracted with ether. After washing with dilute alkali and water, drying (Na_2SO_4), evaporation, and vacuum-distillation, the *ester* (5 g.) had b. p. 116—118°/0·5 mm., n_D^{20} 1·5146 (Found : C, 70·7; H, 7·6. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

Ethyl β-2-*Phenoxyethylglutarate*.—Ethyl 5-phenoxypent-2-enoate (6·8 g.) in dry ethanol (10 c.c.) was added to sodium (0·736 g.) in ethanol (10 c.c.) and ethyl malonate (5·12 g.) at 0°. The solution was stored at 0° for 3 days and then poured into water, made acid with dilute acetic acid, extracted with ether, and dried (Na_2SO_4). The residue was distilled, the substituted malonate (4·6 g.) being collected at 195—200°/0·4 mm. as a viscous oil. Without further purification the tricarboxylic ester (4·6 g.) was hydrolysed for 1 hour with methanolic potassium hydroxide (10%) and then poured into water, and the acid was extracted with ether. The tricarboxylic acid was not obtained crystalline and was decarboxylated at 160—180° for 0·5 hour. The resulting glutaric acid was converted into the *ethyl* ester by boiling ethanol and sulphuric acid (5 hours). The ester (1·8 g.) was distilled; it had b. p. 134—136°/0·004 mm., n_D^{20} 1·4925 (Found : C, 65·7; H, 7·9. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

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