12. *The Synthetic Application of* o-β-*Bromoethylbenzyl Bromide. Part IV. The Preparation of 2-Substituted* 1 : 2 : 3 : 4-*Tetrahydro*isoquinolines.

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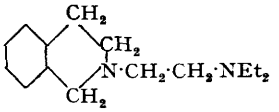
By the condensation of the above bromide with primary amines, a variety of 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*quinolines have been prepared, in which the 2-substituent is an alkyl, aryl, or a heterocyclic group. This reaction constitutes the only practical method by which such 2-aryl derivatives can be prepared.

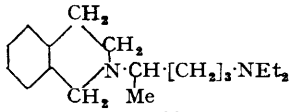
Although the substituents chosen for this preliminary survey are those occurring in other compounds possessing marked physiological activity, the new tetrahydro*iso*quinolines do not reveal any outstanding therapeutic activity.

The condensation of *o*-β-bromoethylbenzyl bromide with aromatic primary amines constitutes the only known practical method whereby 2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines can be prepared (von Braun and Zobel, *Ber.*, 1923, **56**, 2142; Holliman and Mann, J., 1942, 737); a similar condensation also affords an excellent method for the preparation of 2-alkyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines, for which, however, there are other, more laborious methods available (*cf.* Wedekind *et al.*, *Ber.*, 1901, **34**, 3986; 1903, **36**, 1161, 1167; 1909, **42**, 2138; von Braun and Wirtz, *Ber.*, 1927, **60**, 102; Buck *et al.*, *J. Amer. Chem. Soc.*, 1934, **56**, 1769; 1938, **60**, 2101; Allewelt and Day, *J. Org. Chem.*, 1941, **6**, 384). Since *o*-β-bromoethylbenzyl bromide is now readily available (Holliman and Mann, *loc. cit.*), we have made a variety of 2-substituted tetrahydro*iso*quinolines with a view to a rapid preliminary survey of their therapeutic activity. The *iso*quinolyl group is a component of many naturally occurring compounds having notable physiological activity; furthermore, Hjort, de Beer, and Fassett (*J. Pharm.*, 1938, **62**, 165; **63**, 253, 432; 1940, **68**, 69, 73) have found that several 2-alkyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines lower the blood pressure considerably, and thus compare favourably with several natural and artificial drugs in their action as adrenaline-antagonisers.

We have selected for our initial experiments various substituents which in other compounds are associated with marked physiological action. *o*-β-Bromoethylbenzyl bromide reacted readily with *as*-*NN*-diethylethylenediamine to give ultimately the liquid 2-β-*diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (I), characterised as its *dihydrobromide*, *dipicrate*, and *dimethiodide*. 2-Amino-5-diethylamino-*n*-pentane similarly furnished 2-δ-*diethylamino*-α-*methyl*-n-*butyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (II), also characterised as

dihydrobromide and *dipicrate* : the compound (II) contains the alkyl side-chain which is present in plasmoquin and atebrin, and which is therefore intimately associated with their antimalarial properties.


(I.)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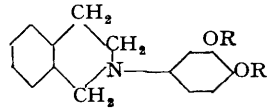
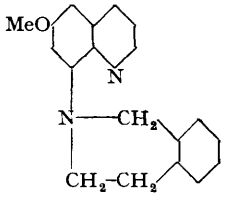
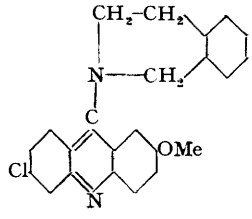

(III.)

For examples of 2-aryl derivatives, the bromide has been condensed with 3 : 4-dimethoxy- and 3 : 4-methylenedioxy-aniline in the presence of potassium carbonate, to furnish 2-(3′ : 4′-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (III; R = Me) and the 2-(3′ : 4′-*methylenedioxyphenyl*) analogue (III; RR = $>CH_2$), respectively. No satisfactory product could be obtained by the attempted demethylation of (III; R = Me). The use of *p*-nitroaniline similarly furnished 2-(p-*nitrophenyl*)*tetrahydro*isoquinoline, from which a number of derivatives might readily be prepared.

(IV.)




(V.)

In order to obtain a compound allied in type to plasmoquin, the bromide was condensed with 8-amino-6-methoxyquinoline in the presence of alcoholic potassium carbonate, furnishing 6-methoxy-8-(2′-1′ : 2′ : 3′ : 4′-tetrahydro*iso*quinolyl)quinoline (IV), isolated as *monohydrochloride* and *monopicrate*.

An attempt to make compounds similarly allied in general type to atebrin has, however, demonstrated certain limitations attending the use of the dibromide for tetrahydro*iso*quinolyl formation. We have attempted to prepare 8-*chloro*-3-*methoxy*-5-(2′-1′ : 2′ : 3′ : 4′-*tetrahydro*isoquinolyl)*acridine* (V) by condensing the dibromide with 8-*chloro*-5-*amino*-3-*methoxyacridine*, but all attempts failed, in spite of a variety of conditions employed. The compound (V) was therefore prepared by the direct condensation of 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline and 5 : 8-dichloro-3-methoxyacridine in boiling toluene, a method for which we are indebted to Dr. D. Muriel Hall of Bedford College (University of London); it was also obtained by heating these reagents with a mixture of phenol and potassium carbonate, but the yield was low owing to contamination with 8-chloro-5-phenoxy-3-methoxyacridine. The last method has, however, been successfully used to prepare the isomeric 8-*chloro*-3-*methoxy*-5-(1′-1′ : 2′ : 3′ : 4′-*tetrahydroquinolyl*)*acridine* from tetrahydroquinoline.

The therapeutic properties of these compounds have been investigated by the staff of Imperial Chemical Industries Ltd. (Biological Department) at Blackley. The compounds (I), (III; R = Me) and (III; RR = $>CH_2$) have been submitted to general tests, including a toxicity test in mice, a " chronic " toxicity test (*i.e.*, repeated dosage) in rats with subsequent examination of the organs, and a test on rabbit intestine : their effect on the blood pressure of the rabbit has also been examined. Toxicity was low, and the compounds did not reveal any outstanding physiological action. The dihydrobromide of (II), the hydrochloride of (IV), and the two acridines were tested for their action against *P. gallinaceum* infection in chicks, but were inactive.

Experimental.

2-β-*Diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (I).—*as.*-*NN*-Diethylethylenediamine (3 c.c.; prepared by Mann's method, J., 1927, 2910) was added with stirring to powdered *o*-β-bromoethylbenzyl bromide (2·4 g.); a vigorous reaction, with much heat evolution, ensued. The cold glassy product, when heated with alcohol (40 c.c.), readily crystallised, a further crop separating as the mixture cooled. The united product, recrystallised from alcohol, furnished the *dihydrobromide* of (I), colourless crystals, m. p. 207—209° (Found : C, 46·2; H, 6·5; N, 7·0; Br, by Carius, 40·7; Br, ionic, 40·5. $C_{15}H_{24}N_2$,2HBr requires C, 45·7; H, 6·6; N, 7·1; Br, 40·6%). Treatment of this compound with excess of picric acid, both in alcoholic solution, gave the *dipicrate* of (I), yellow crystals from alcohol–acetone, softening at 130°, m. p. 167—171° (decomp.) (Found : C, 47·3; H, 4·4; N, 16·4. $C_{15}H_{24}N_2$,2$C_6H_3O_7N_3$ requires C, 47·95; H, 4·35; N, 16·2%).

Basification of an aqueous solution of the dihydrobromide, followed by ether extraction and distillation, gave the iso*quinoline* (I) as a colourless mobile oil, b. p. 166—167°/14 mm. (Found : C, 77·8; H, 10·5; N, 12·2. $C_{15}H_{24}N_2$ requires C, 77·6; H, 10·3; N, 12·1%); this combined readily with methyl iodide, and the final sticky product solidified when triturated with ether; recrystallisation from alcohol furnished colourless crystals of the *dimethiodide* of (I), m. p. 183—185° (Found : C, 39·4; H, 6·05; N, 5·2. $C_{17}H_{30}N_2I_2$ requires C, 39·5; H, 5·8; N, 5·4%).

2-δ-*Diethylamino*-α-*methyl*-n-*butyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (II).—When 2-amino-5-diethylamino-*n*-pentane (4·9 g., 6·6 c.c.) was added to the bromide (8·4 g., 1 mol.) vigorous reaction ensued, which was controlled by external cooling. The cold, hygroscopic, glassy product was dissolved in hot alcohol, and ether added until the solution was turbid; slow cooling now gave crystals of the *dihydrobromide* of (II), which, after a repetition of the alcohol–ether treatment, had m. p. 190—192° with preliminary softening (Found : C, 49·4; H, 7·6; N, 6·5; Br, by Carius, 37·0; Br, ionic, 36·8. $C_{18}H_{30}N_2$,2HBr requires C, 49·55; H, 7·3; N, 6·4; Br, 36·7%). Basification of an aqueous solution, followed by ether extraction, furnished the liquid iso*quinoline* (II), b. p. 200°/16 mm. (Found : C, 78·9; H, 11·4; N, 10·5. $C_{18}H_{30}N_2$ requires C, 78·8; H, 10·95; N, 10·2%).

The original preparation was repeated but with an excess (3 mols.) of the aminopentane. An ethereal extract of the cold reaction product was dried (potassium hydroxide), and on fractional distillation furnished the pure *iso*quinoline (II) directly.

Mixing of alcoholic solutions of (II) and of picric acid precipitated the sticky semi-solid *dipicrate*, which solidified on long boiling with alcohol, and was then recrystallised from alcohol–acetone; yellow leaflets, m. p. 150—151° (Found: C, 50·0; H, 5·5; N, 16·0. $C_{18}H_{30}N_2,2C_6H_3O_7N_3$ requires C, 49·2; H, 4·9; N, 15·3%). Methyl iodide reacted vigorously with the free base (II), but the deliquescent sticky product could not be crystallised.

No products similar in type to (I) and (II) could be isolated by the condensation of the dibromide with αγ-diamino-β-hydroxypropane or with *NN'*-di-(β-aminoethyl)ethylenediamine, $C_2H_4(NH{\cdot}C_2H_4{\cdot}NH_2)_2$.

2-(3′ : 4′-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (III; R = Me).—Pyrocatechol was methylated to veratrole by Ullmann's method (*Annalen*, 1903, **327**, 115), which was found to be much superior to that of Perkin and Weizmann (J., 1906, **89**, 1649). The nitration and subsequent reduction of veratrole were performed by Moureu's method (*Bull. Soc. chim.*, 1896, **15**, 647): Moureu decomposed the chlorostannate of the 3 : 4-dimethoxyaniline with hydrogen sulphide, but we found it advantageous to decompose this salt with aqueous sodium hydroxide, and extract the liberated amine repeatedly with ether. A powdered, intimate mixture of the bromide (15 g.), 3 : 4-dimethoxyaniline (8 g., 1 mol.), and potassium carbonate (12 g., 1·6 mols.) was heated in an oil-bath until effervescence began. The mixture was removed from the bath until the reaction subsided, and was then reheated at 130° for 30 minutes. An acetone extract of the cold pulverised product, when filtered and evaporated, gave a solid residue which, recrystallised from alcohol, furnished colourless needles of the iso*quinoline* (III; R = Me), m. p. 94—95° (Found: C, 76·0; H, 7·05; N, 5·3. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%). A mixture of this base (1·5 g.), hydriodic acid of constant b. p. (5 c.c.), and acetic acid (20 c.c.) was refluxed gently for 3 hours. The cold product when neutralised gave a sticky solid which could neither be crystallised nor converted into a crystalline picrate.

2-(3′ : 4′-*Methylenedioxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (III; RR = >CH_2).—The 3 : 4-methylenedioxyaniline used was prepared from piperonal by the method of Rupe and Majewski (*Ber.*, 1900, **33**, 3401) (cf. Buck and Ide, *Org. Syn.*, 1935, **15**, 58). An intimate mixture of the bromide (2·8 g.), 3 : 4-methylenedioxyaniline (1·37 g., 1 mol.), and anhydrous sodium carbonate (4 g., 3·8 mols.) was heated at 130° for 15 minutes. An ethereal extract of the cold pulverised product when evaporated gave an oil (2·5 g., 99%) which rapidly solidified; recrystallisation from alcohol gave colourless needles of the iso*quinoline*, m. p. 58° (Found: C, 75·8; H, 6·0; N, 5·5. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9; N, 5·5%). The *picrate* was prepared in and recrystallised from alcohol; m. p. 135° (Found: C, 54·8; H, 3·8; N, 11·5. $C_{16}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 54·8; H, 3·7; N, 11·6%).

2-(p-*Nitrophenyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—A mixture of the bromide (2·8 g.), *p*-nitroaniline (1·38 g., 1 mol.), and potassium carbonate (4 g., 2·9 mols.) was heated at 150° for 15 minutes; as the temperature rose to this value, no effervescence was detected, but steam was evolved at *ca.* 100° and the mixture darkened in colour at 110—120°. The final orange-coloured product was cooled, crushed, extracted with cold water, and the residue recrystallised from alcohol; the iso*quinoline* (1·2 g., 48%) was thus obtained as yellow plates, m. p. 152—154° (Found: C, 71·2; H, 5·7; N, 10·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%).

Alternatively, the above mixture was added to alcohol (20 c.c.) and refluxed for 6 hours. Hot alcohol (50 c.c.) was then added, and the product filtered off and extracted repeatedly with hot alcohol. The combined filtrate and washings were concentrated to *ca.* 50 c.c. and cooled; the *iso*quinoline (0·8 g.) crystallised on cooling, and when collected, washed with alcohol and water, and dried, was pure; m. p. 152—154°.

6-*Methoxy*-8-(2′-1′ : 2′ : 3′ : 4′-*tetrahydro*isoquinolyl)*quinoline* (IV).—A mixture of the bromide (8·4 g.), 8-amino-6-methoxyquinoline (4·8 g., 1 mol.), potassium carbonate (12 g.), and alcohol (120 c.c.) was refluxed for 6 hours, and then filtered whilst hot. The residue was washed with hot alcohol, and the united filtrates evaporated. The residual oil was dissolved in ether, the solution shaken with water and dried (sodium sulphate). After evaporation of the ether, fractional distillation gave an oil, b. p. 190—210°/0·05 mm., presumably the *iso*quinoline (IV). On cooling, however, it formed a glass which could not be crystallised; it was therefore dissolved in warm concentrated hydrochloric acid, and the solution on cooling deposited crystals of the *monohydrochloride* of (IV). This salt was collected, dried, and recrystallised from alcoholic ether, from which the *monohydrate* separated as hard yellowish-brown crystals, m. p. 145—147° (Found: C, 66·3; H, 6·2; N, 8·1; Cl, 10·2. $C_{19}H_{18}ON_2,HCl,H_2O$ requires C, 66·2; H, 6·1; N, 8·1; Cl, 10·3%). This hydrate possessed considerable thermal stability, and when heated at 100°/15 mm. for 5·5 hours lost only 70% of its water, which was slowly re-absorbed on exposure to cold air. The salt is only moderately soluble in cold water, and the solution develops a marked opacity, presumably by dissociation.

When an alcoholic solution of the above distillate was treated with alcoholic picric acid, a *monopicrate* was precipitated which was almost insoluble in boiling alcohol, but recrystallised from alcoholic acetone containing free picric acid as yellow crystals, m. p. 183° (decomp.) (Found: C, 58·8; H, 4·5; N. 14·8. $C_{19}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 57·8; H, 4·05; N, 13·5%. $C_{19}H_{18}ON_2,2C_6H_3O_7N_3$ requires C, 49·7; H, 3·2; N, 15·0%).

8-*Chloro*-5-*amino*-3-*methoxyacridine*.—A current of dry ammonia was passed through a solution of 5 : 8-dichloro-3-methoxyacridine (2 g.) in phenol (5 g.) at 160° for 15 minutes. The semi-solid mass was cooled, triturated with ether, and the residual *aminoacridine hydrochloride* (2·7 g.) was collected, washed again with ether, and recrystallised from 50% aqueous alcohol; canary-yellow crystals, m. p. 349—350° (decomp.) (Found: C, 56·3; H, 4·0; N, 9·6. $C_{14}H_{11}ON_2Cl,HCl$ requires C, 56·95; H, 4·1; N, 9·5%).

A small excess of aqueous sodium hydroxide was added to a boiling alcoholic solution of this hydrochloride, and the whole was then poured into much water. The precipitated 8-*chloro*-5-*amino*-3-*methoxyacridine* was collected, washed with water, and purified by dissolution in much boiling alcohol, to which water was then cautiously added until a turbidity appeared; slow cooling deposited the acridine as yellowish-brown plates, m. p. 274° (Found: C, 64·6; H, 4·5; N, 10·6. $C_{14}H_{11}ON_2Cl$ requires C, 65·0; H, 4·25; N, 10·8%).

8-*Chloro*-3-*methoxy*-5-(2′-1′ : 2′ : 3′ : 4′-*tetrahydro*isoquinolyl)*acridine* (V).—Preliminary experiments showed that when an alcoholic solution containing equimolecular quantities of the bromide and 8-chloro-5-amino-3-methoxyacridine hydrochloride was refluxed with an excess of potassium carbonate for 6 hours, the acridine was unchanged. A dry mixture of the bromide (1·4 g.), the free amino-acridine (1·3 g., 1 mol.), and potassium carbonate (2 g.) was therefore heated at 140—150° for 10 minutes, by which time it had developed a reddish-brown colour but no effervescence was detected. The cold pulverised product was thoroughly extracted with cold water and alcohol in turn, but the yellow residue proved to be 8-*chloro*-5-*amino*-3-*methoxyacridine hydrobromide*; it was insoluble in all solvents tried, and before analysis was further washed first with boiling alcohol and then with hot water (Found: C, 50·2; H, 3·6; N, 8·6; Cl + Br, 32·6. $C_{14}H_{11}ON_2Cl,HBr$ requires C, 49·5; H, 3·5; N, 8·25; Cl + Br, 34·1%).

The acridine (V) was therefore prepared by the following methods. (A) A mixture of 5 : 8-dichloro-3-methoxyacridine (2·8 g.), 1 : 2 : 3 : 4-tetrahydro*iso*quinoline (2·8 g., 2 mols.) and toluene (40 c.c.) was refluxed for 36 hours, and the tetrahydro*iso*quinoline hydrochloride which had separated was filtered off from the hot solution. The filtrate on cooling deposited the *acridine* (V) (1·6 g.), which was recrystallised from alcohol; yellow crystals, m. p. 178—181° (Found: C, 73·5; H, 4·7; N, 7·7. $C_{23}H_{19}ON_2Cl$ requires C, 73·7; H, 5·05; N, 7·5%).

(B) A mixture of the dichloroacridine (2·8 g.) and phenol (12 g.) was heated on a water-bath until a solution was obtained. Potassium carbonate (0·7 g.) and the *iso*quinoline (1·33 g., 1 mol.) were added in turn. Carbon dioxide was vigorously evolved, and the mixture became orange. After 2 hours' heating, the cold product was poured with vigorous

stirring into 10% aqueous sodium hydroxide solution. The aqueous layer was decanted, and the semi-solid residue, when triturated with ether, gave a yellow powder (2·1 g.). This was collected, washed with alcohol and water, and dried. Recrystallisation from alcohol and then from ethyl acetate ultimately gave the pure acridine (V), m. p. **179**—180°, unchanged by admixture with that prepared by method (A). Several similar experiments showed that the crude product obtained by method (B) was contaminated with the intermediate 8-chloro-5-phenoxy-3-methoxyacridine, the presence of which necessitated the repeated and wasteful recrystallisation. Method (B) is essentially that developed by Burckhalter, Jones, Holcomb, and Sweet (*J. Amer. Chem. Soc.*, 1943, **65**, 2012).

8-*Chloro*-3-*methoxy*-5-(1′-1′ : 2′ : 3′ : 4′-*tetrahydroquinolyl*)*acridine.*—This preparation was precisely similar to (B) above, but utilised 1 : 2 : 3 : 4-tetrahydroquinoline (1·33 g.). After the mixture had been heated on the water-bath for 3 hours, it was cooled and poured with stirring into 10% aqueous sodium hydroxide (60 c.c.). The red, viscous, insoluble solid was now extracted with ether (in which it was readily soluble), and the extract thoroughly washed with very dilute acetic acid and then with water, and finally dried (sodium sulphate). After complete removal of the ether, the residue readily solidified, and after recrystallisation from alcohol furnished yellow crystals (1·7 g.) of the above *acridine*, m. p. **169**—171° (Found : C, 73·75; H, 5·4; N, 7·25%). The omission of potassium carbonate from the original reaction mixture caused a marked decrease in the yield of the acridine.

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