371. *Contributions to the Chemistry of* isoQuinolines. *Part II. The Synthesis of Chloro-amino-phenyl*isoquinolines *in a Search for New Trypanocides.*

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In furtherance of earlier studies (*J.*, 1949, 696) and by similar methods, 7-amino-1-*p*-chlorophenyl- and 7-chloro-1-*p*-aminophenyl-*iso*quinoline methiodides have been synthesised. They showed no noteworthy biological activity.

In Part I (*J.*, 1949, 696) it was shown that nitration of 3 : 4-dihydro*iso*quinolines introduced a nitro-group at the 7-position. This substitution appeared to lend itself readily to the synthesis of 7-chloro*iso*quinolines which are of interest in view of the occurrence of the *p*-chlorophenyl group in a number of biologically active products.

The required 3 : 4-dihydro*iso*quinolines were obtained by Bischler–Napieralski cyclisation of the requisite carboxyamides in toluene or tetralin by means of phosphoric oxide, *viz.*, *p*-chlorobenzo-2-phenylethylamide to 1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline, *N*-*p*-chlorobenzo-2-*p*-chlorophenylethylamide to 7-chloro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline, *N*-*p*-nitro-

benzo-2-*p*-chlorophenylethylamide to 7-chloro-1-*p*-nitrophenyl-3 : 4-dihydro*iso*quinoline. In addition, 4-chloro-3-nitrobenzo-2′-phenylethylamide was cyclised to 1-(4′-chloro-3′-nitrophenyl)-3 : 4-dihydro*iso*quinoline during investigations into the structure of nitration products.

Nitration of 1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline under mild conditions has been found to occur at the 7-position since reduction of the product to the amine, followed by a Sandmeyer reaction, gave 7-chloro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline, identical with the product of cyclisation of *p*-chlorobenzo-2-*p*-chlorophenylethylamide. Further nitration introduced a second nitro-group to give a product, also obtained in one step by use of a stronger nitrating mixture, identical with the nitration product of 1-(4′-chloro-3′-nitrophenyl)-3 : 4-dihydro*iso*quinoline, thus establishing the point of entry of this second nitro-group.

The 3 : 4-dihydro*iso*quinolines were dehydrogenated by palladium black to the *iso*quinolines, which were either reduced to the corresponding amines, or were methylated, before reduction, to give the corresponding quaternary salts. 1-*p*-Aminophenyl*iso*quinoline (Gilman and Gainer, *J. Amer. Chem. Soc.*, 1947, **69**, 1946) and its methiodide were similarly prepared from 1-*p*-nitrophenyl*iso*quinoline..

None of these bases or quaternary salts showed noteworthy activity against *Trypanosoma equiperdum*, *T. congolense*, or *Entamœba histolytica*.

Experimental.

p-*Chlorophenylethylamine*.—*β*-*p*-Chlorophenylpropionic acid (Shoppee, *J.*, 1930, 976) (80 g.) was refluxed with thionyl chloride (80 c.c.) for 3 hours and excess of thionyl chloride was removed under reduced pressure. The product was added portion-wise to a stirred solution of sodium azide (56 g.) in 50% acetone (1 l.) maintained at 0°, and the mixture, which separated into two layers, was extracted with benzene. The benzene extract was thoroughly dried ($CaCl_2$) at 0° and was then refluxed until nitrogen evolution ceased. Hydrochloric acid (*d* 1·16; 80 c.c.) was added and refluxing continued until carbon dioxide evolution ceased. The amine hydrochloride which separated was redissolved in water, and the benzene separated. The aqueous layer was basified and the amine extracted with ether. The extract was dried (K_2CO_3) and distilled, yielding a colourless oil (62·6 g., 92·8%), b. p. 125—130°/10 mm. Buch (*J. Amer. Chem. Soc.*, 1933, **55**, 2593) obtained a 50% yield by catalytic reduction of carbomethoxy-*p*-chloromandelonitrile. The *toluene*-p-*sulphonate* crystallised from alcohol in white plates, m. p. 235° (Found : N, 4·2; Cl, 11·1. $C_{15}H_{16}O_2NClS$ requires N, 4·5; Cl, 11·5%).

N-*Acyl*-2-*phenylethylamides*.—2-Phenylethylamine, or its *p*-chloro-derivative (1 mol.), was dissolved in 50% acetone (20 parts), and the appropriate acid chloride (0·5 mol.) added in small portions with shaking and cooling. 2N-Sodium hydroxide (1·5 equivs.) was added and a further quantity of the acid chloride (0·7 mol.) added portionwise as before. The solution was diluted and filtered and the product crystallised from ethanol. The following were thus prepared (yields in parentheses) : p-*nitrobenzo*-2-p-*chlorophenylethylamide* (72%), m. p. 148° (Found : N, 8·8; Cl, 11·3. $C_{15}H_{13}O_3N_2Cl$ requires N, 9·2; Cl, 11·7%); p-*chlorobenzo*-2-p-*chlorophenylethylamide* (74%), m. p. 147° (Found : N, 4·8; Cl, 23·8. $C_{15}H_{13}ONCl_2$ requires N, 4·8; Cl, 24·1%) [*p*-chlorobenzoic anhydride, m. p. 193°, was isolated as an insoluble by-product (Found : Cl, 23·6. Calc. for $C_{14}H_8O_3Cl_2$: Cl, 24·1%); cf. Frankland, Carter, and Adams, *J.*, 1912, **101**, 2479; Oden, *Chem. Zentr.*, 1919, III, 541]; p-*chlorobenzo*-2-*phenylethylamide* (78%), m. p. 134° (Found : N, 5·5; Cl, 13·6. $C_{15}H_{14}ONCl$ requires N, 5·4; Cl, 13·7%); and 4-*chloro*-3-*nitrobenzo*-2′-*phenylethylamide* (44%), m. p. 96° (Found : N, 9·3; Cl, 11·2. $C_{15}H_{13}O_3N_2Cl$ requires N, 9·2; Cl, 11·7%).

3 : 4-*Dihydro*isoquinolines.—The appropriate carboxyamide (1 part) and phosphoric oxide (5 parts) were refluxed in tetralin or toluene (25 parts) for 30—45 minutes. The product was decomposed with water, the aqueous layer separated and basified, and the precipitate crystallised or distilled. The following were thus prepared (yields in parentheses) : 1-p-*chlorphenyl*-3 : 4-*dihydro*isoquinoline (90%), m. p. 77°, b. p. 160—165 (bath-temp.)/0·1 mm., white prisms from light petroleum (b. p. 80—100°) (Found : N, 5·7; Cl, 14·5. $C_{15}H_{12}NCl$ requires N, 5·8; Cl, 14·7%) [*hydrochloride*, white plates (from alcohol), m. p. 235—237° (Found : N, 4·8; Cl, 25·5. $C_{15}H_{12}NCl,HCl$ requires N, 5·0; Cl, 25·6%)]; 7-*chloro*-1-p-*chlorophenyl*-3 : 4-*dihydro*isoquinoline (32%), m. p. 65—66°, b. p. 180—185° (bath-temp.)/0·05 mm., white prisms from light petroleum (b. p. 80—100°) (Found : N, 5·1; Cl, 25·2. $C_{15}H_{11}NCl_2$ requires N, 5·1; Cl, 25·7%) [*hydrochloride*, white plates (from alcohol), m. p. 237° (Found : N, 4·2; Cl, 34·1. $C_{15}H_{11}NCl_2,HCl$ requires N, 4·5; Cl, 34·0%)]; 7-*chloro*-1-p-*nitrophenyl*-3 : 4-*dihydro*isoquinoline (47%), yellowish prisms (from ethanol), m. p. 148° (Found : C, 62·9; H, 4·0; N, 9·9. $C_{15}H_{11}O_2N_2Cl$ requires C, 62·8; H, 3·8; N, 9·8%), and 1-(4′-chloro-3′-nitrophenyl)-3 : 4-dihydro-*iso*quinoline (48% as picrate), b. p. 200—210° (bath-temp.)/0·2 mm. [*picrate*, yellow prisms (from acetone–alcohol), m. p. 196° (sinters at 170°) (Found : N, 13·8; Cl, 7·1. $C_{21}H_{14}O_9N_5Cl$ requires N, 13·6; Cl, 6·9%)]. The base was regenerated from the picrate (3·6 g.) by shaking this salt with ether and saturated aqueous lithium hydroxide and was obtained as an oil (2·1 g.) which slowly solidified at 0° to a pale yellow solid, m. p. 62—63°.

7-*Nitro*-1-p-*chlorophenyl*-3 : 4-*dihydro*isoquinoline.—1-*p*-Chlorophenyl-3 : 4-dihydro*iso*quinoline (5 g.) was dissolved in nitric acid (*d* 1·4; 25 c.c.) and nitric acid (*d* 1·5; 50 c.c.) was added slowly with stirring and the solution set aside overnight. The solution was poured on ice and basified, and the precipitate filtered and crystallised from alcohol in pale yellow prisms (4·6 g., 77%), m. p. 137° (Found : C, 62·8; H, 3·8. $C_{15}H_{11}O_2N_2Cl$ requires C, 63·1; H, 4·1%). The *picrate* crystallised from alcohol in yellow needles, m. p. 160—170°, then solidifying, and remelting at 191° (Found : C, 49·1; H, 2·8. $C_{21}H_{14}O_9N_5Cl$ requires C, 48·9; H, 2·7%).

7-Nitro-1-(*4'-chloro-3'-nitrophenyl*)-3 : 4-*dihydro*iso*quinoline*.—(*A*) 1-*p*-Chlorophenyl-3 : 4-dihydro*iso*quinoline (1·2 g.) was dissolved in sulphuric acid (*d* 1·84; 4 c.c.) and a solution of potassium nitrate (1·5 g.) in sulphuric acid (*d* 1·84; 10 c.c.) was slowly added. The mixture was set aside overnight and then poured on ice and basified. The precipitated iso*quinoline* was filtered off and crystallised from alcohol in pale yellow needles (1·5 g., 91%), m. p. 108° (Found: C, 54·3; H, 3·0; N, 12·9. $C_{15}H_{10}O_4N_3Cl$ requires C, 54·3; H, 3·0; N, 12·7%). The *picrate* crystallised from acetone in yellow prisms, m. p. 214—215° (Found: N, 14·8; Cl, 6·2. $C_{21}H_{13}O_{11}N_6Cl$ requires N, 15·0; Cl, 6·3%).

(*B*) 7-Nitro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline (0·7 g.) was nitrated by the method described in (*A*). The product crystallised from alcohol in pale yellow needles (1·6 g.), m. p. 108° showing no depression on admixture with the product from (*A*).

(*C*) 1-(4'-Chloro-3'-nitrophenyl)-3 : 4-dihydro*iso*quinoline (1 g.) was nitrated by the method described in (*A*). The product crystallised from alcohol in pale yellow needles, m. p. 108°, showing no depression on admixture with the product from (A). The picrate had m. p. 214—215° and showed no depression on admixture with the above salt.

7-Amino-1-p-*chlorophenyl*-3 : 4-*dihydro*iso*quinoline*.—7-Nitro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline (5 g.) was refluxed in 5N-hydrochloric acid (120 c.c.) while iron dust (14 g.) was added portion-wise as rapidly as possible. The mixture was refluxed for 1 hour; crystals separated on cooling; these were redissolved and the solution was basified with aqueous ammonia and filtered. The residue was repeatedly extracted with hot alcohol, and the extract was evaporated to small bulk, diluted with water, extracted with ether, and dried. The ether was removed and the residue (2·25 g.) was crystallised from benzene–alcohol in pale yellow needles, m. p. 183° (Found: N, 11·0; Cl, 13·8. $C_{15}H_{13}N_2Cl$ requires N, 10·9; Cl, 13·9%). The *dihydrochloride* crystallised from alcohol in greenish prisms, m. p. 283° (Found: C, 54·6; H, 4·7; N, 8·6; Cl, 31·8. $C_{15}H_{13}N_2Cl,2HCl$ requires C, 54·6; H, 4·6; N, 8·5; Cl, 32·3%).

Proof of the Structure of 7-Amino-1-p-*chlorophenyl*-3 : 4-*dihydro*iso*quinoline*.—7-Amino-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline dihydrochloride (1·25 g.), dissolved in 2N-hydrochloric acid (5 c.c.), was diazotised at 0° with sodium nitrite (0·3 g.) in water (2 c.c.). After 15 minutes the solution was poured into a solution of cuprous chloride (1 g.) in hydrochloric acid (*d* 1·16; 20 c.c.) at 0°. Nitrogen was evolved rapidly and the solution was heated at 60° for 15 minutes. Excess of aqueous ammonia was added, the solution extracted with chloroform, and the extract washed with water and dried. The product was distilled [b. p. 180—190° (bath-temp.)/0·5 mm.] and the distillate converted into the hydrochloride (0·5 g.), m. p. 236—237°, which showed no depression on admixture with 7-chloro-1-*p*-chlorophenyl-3 : 4-dihydro*iso*quinoline hydrochloride, m. p. 237°. The regenerated base had m. p. 64—65° showing no depression on admixture with authentic material. The *picrate* crystallised from alcohol in yellow prisms, m. p. 152° (Found: N, 11·3; Cl, 13·9. $C_{21}H_{14}O_7N_4Cl_2$ requires N, 11·1; Cl, 14·1%).

Dehydrogenations.—The dihydro-base was intimately mixed with 10% of palladium black and heated in 1-g. portions for an appropriate time and temperature indicated in parentheses. The melt was powdered, extracted with hydrochloric acid, and filtered, and the filtrate was basified. The precipitate was crystallised from alcohol–acetone. Yields are indicated in parentheses. The following were thus obtained: *7-Nitro*-1-p-*chlorophenyl*iso*quinoline* (210—220°; 2 minutes), yellow needles (48%), m. p. 209° (Found: C, 63·7; H, 3·5; N, 9·8. $C_{15}H_9O_2N_2Cl$ requires C, 63·3; H, 3·2; N, 9·8%); *7-chloro*-1-p-*nitrophenyl*iso*quinoline* (210—215°; 10 minutes), yellow needles (44%), m. p. 176° (Found: C, 63·3; H, 3·3; N, 10·1. $C_{15}H_9O_2N_2Cl$ requires C, 63·3; H, 3·2; N, 9·8%), and *7-nitro*-1-(*4'-chloro-3'-nitrophenyl*)iso*quinoline* (230°; 20 minutes), brown needles (48%), m. p. 221° (Found: N, 12·9; Cl, 10·5. $C_{15}H_8O_4N_3Cl$ requires N, 12·8; Cl, 10·8%).

Quaternisations.—The base was dissolved in nitrobenzene at 150°, methyl sulphate (2 mols.) added, and the mixture allowed to cool. The solution was diluted with ether and extracted with minimal amounts of water, and the methiodide precipitated by addition of excess of potassium iodide. Thus were obtained *7-nitro*-1-p-*chlorophenyl*iso*quinoline methiodide*, small brown plates, m. p. 228—229° (decomp.) (90%) (Found: N, 6·7; I, 29·8. $C_{16}H_{12}O_2N_2ClI$ requires N, 6·6; I, 29·8%), *7-chloro*-1-p-*nitrophenyl*iso*quinoline methiodide*, orange needles (82%), m. p. 235—236° (decomp.) (Found: N, 6·8. $C_{16}H_{12}O_2N_2ClI$ requires N, 6·6%), and 1-p-*nitrophenyl*iso*quinoline methiodide*, yellow prisms (79%), m. p. 244° (Found: N, 7·1; I, 32·7. $C_{16}H_{13}O_2N_2I$ requires N, 7·1; I, 32·4%).

Reductions.—(A) *Nitro-bases*. The nitro-base (1 part) was dissolved in boiling 5N-hydrochloric acid (25 parts), iron dust (3 parts) added as rapidly as possible, and the mixture refluxed for 1 hour. The hot solution was filtered and the filtrate basified with excess of aqueous ammonia and filtered. The residue was extracted with hot alcohol, and the extract evaporated to small bulk and diluted with water. The base was taken up in ether and precipitated as the dihydrochloride which was crystallised from methanol. Thus were obtained *7-chloro*-1-p-*aminophenyl*iso*quinoline dihydrochloride*, red needles (78%), m. p. indefinite (softens at 250°, resolidifies and remelts at 288—290°) (Found: C, 52·9; H, 4·6; N, 8·2; loss at 100°/1 mm., 4·9. $C_{15}H_{11}N_2Cl,2HCl,H_2O$ requires C, 52·1; H, 4·3; N, 8·1; loss, 5·2%) [the *base* crystallised from light petroleum (b. p. 80—100°) in pale yellow needles, m. p. 112—113° (Found: C, 70·1; H, 4·5; N, 11·3. $C_{15}H_{11}N_2Cl$ requires C, 70·7; H, 4·3; N, 11·0%)], and *7-amino*-1-p-*chlorophenyl*-iso*quinoline dihydrochloride*, sandy prisms (71%), m. p. 305° (Found: C, 54·3; H, 4·0; N, 8·9. $C_{15}H_{11}N_2Cl,2HCl$ requires C, 55·0; H, 4·0; N, 8·5%).

(B) *Quaternary salts*. The nitro-derivative (1 part) was dissolved in hot water (60 parts) containing 2N-hydrochloric acid (2 parts) and was added to a stirred boiling suspension of reduced iron (1 part) in water (60 parts). The mixture was refluxed for 1·5 hours and then filtered and the iron precipitated by a slight excess of aqueous ammonia. The filtrate was evaporated to small bulk and filtered, and the methiodide precipitated by addition of solid potassium iodide and crystallised from hot water. Thus were obtained *7-amino*-1-p-*chlorophenyl*iso*quinoline methiodide*, yellow needles (87%), m. p. 262° (Found: N, 7·2; I, 31·9. $C_{16}H_{14}N_2ClI$ requires N, 7·1; I, 32·0%), *7-chloro*-1-p-*aminophenyl*iso*quinoline methiodide*, orange needles (77%) of indefinite m. p. (sinters at 143—145° and melts *ca.* 155°) (Found: C, 46·6; H, 4·0; N, 7·1; loss at 100°/10 mm., 3·3. $C_{16}H_{14}N_2ClI,H_2O$ requires C, 46·3; H, 3·9; N, 6·8; loss, 4·3%), and 1-p-*aminophenyl*iso*quinoline methiodide*, yellow prisms (71%), m. p. 206° (Found: N, 7·8; I, 35·3. $C_{16}H_{15}N_2I$ requires N, 7·7; I, 35·1%).

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