54. *Synthetic Antimalarials. Part XXXV. Further Arylamino-dialkylaminoalkylaminoquinoline Derivatives.*

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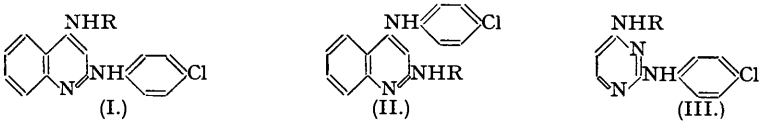
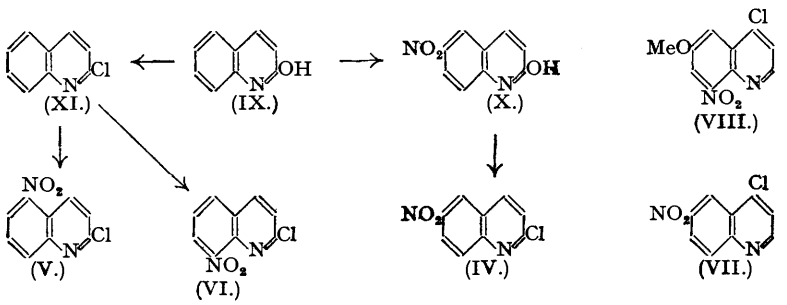
The synthesis of a number of arylamino-dialkylaminoalkylaminoquinolines having the arylamino- and dialkylaminoalkylamino-groups attached to different rings in the quinoline nucleus has been attempted. Several such compounds have been prepared, but none has been found to possess significant antimalarial activity.

The synthesis of quinoline drivatives of types (I) and (II) (R = dialkylaminoalkyl), in which the two substituents are attached to the pyridine ring of the quinoline nucleus, has been described by Curd, Raison, and Rose (Part XVII, *J.*, 1947, 899), and it has been shown that, of these, the compounds of type (I) are the more active as antimalarials and, further, that their activity is most probably due not to their representation as modified 4-dialkylaminoalkylaminoquinolines, but rather to their biological relationship to the pyrimidines of type (III). The preparation of similarly substituted quinolines, in which the two groups are attached to different rings, forms the subject of the present communication.

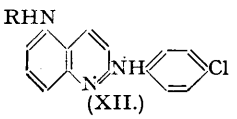


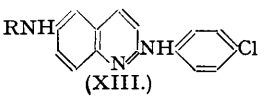
For the synthesis of compounds having the arylamino-group in the pyridine ring, the five chloronitroquinolines (IV, V, VI, VII, and VIII) were used as intermediates. Nitration of 2-hydroxyquinoline (IX) followed by reaction of the product, 6-nitro-2-hydroxyquinoline (X), with phosphorus pentachloride gave 2-chloro-6-nitroquinoline (IV). 2-Chloro-5-nitroquinoline (V) and 2-chloro-8-nitroquinoline (VI) were prepared by nitration of 2-chloroquinoline (XI) and partially separated by recrystallisation from benzene. It was found best not to attempt to purify these compounds completely, but to use them in their crude condition in the subsequent reaction with *p*-chloroaniline, since the resulting *nitro*-p-*chloroanilinoquinolines* are easily purified by crystallisation. 4-Chloro-6-nitroquinoline (VII) and 4-chloro-8-nitro-6-methoxyquinoline (VIII) were prepared from *p*-nitroaniline and 2-nitro-4-methoxyaniline respectively by condensation with ethyl ethoxymethylenemalonate to give ethyl *p*-nitroanilinomethylenemalonate and ethyl 2-nitro-4-methoxyanilinomethylenemalonate, which were cyclised in boiling diphenyl ether to ethyl 6-nitro-4-hydroxyquinoline-3-carboxylate and ethyl 8-nitro-4-hydroxy-6-methoxyquinoline-3-carboxylate respectively (Riegel *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1264, 1267). These esters were hydrolysed to the corresponding acids and decarboxylated by pyrolysis of the silver salts in boiling diphenyl ether to give 6-nitro-4-hydroxyquinoline and 8-nitro-4-hydroxy-6-methoxyquinoline, which were converted into the chloro-compounds (VII) and (VIII) by phosphorus oxychloride. The five chloronitroquinolines (IV, V, VI, VII, and VIII) were each heated with *p*-chloroaniline, either without a solvent or in xylene solution, the reactions varying considerably in the ease with which they took place. The resulting products, namely 6-, 5-, and 8-*nitro*-2-p-*chloroanilinoquinoline*, 6-*nitro*-4-p-*chloroanilinoquinoline*, and 8-*nitro*-4-p-*chloroanilino*-6-*methoxyquinoline*, were reduced with stannous chloride and hydrochloric acid to the corresponding *amino*-p-*chloroanilinoquinolines*.

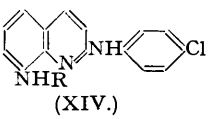


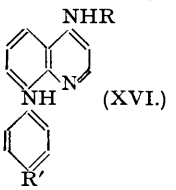
The diethylaminoethyl group was introduced into 5-*amino*-2-p-*chloroanilinoquinoline* and 8-*amino*-2-p-*chloroanilinoquinoline* by heating them with diethylaminoethyl chloride in xylene to give 2-p-*chloroanilino*-5-β-*diethylaminoethylaminoquinoline* (XII, R = $CH_2 \cdot CH_2 \cdot NEt_2$) and 2-p-*chloroanilino*-8-β-*diethylaminoethylaminoquinoline* (XIV, R = $CH_2 \cdot CH_2 \cdot NEt_2$) respectively. Although good yields were obtained, the formation of tarry substances made the working up of the products difficult, and subsequently diethylaminoethyl chloride hydrochloride was used. Application of this method to 6-*amino*-2-p-*chloroanilinoquinoline* gave 2-p-*chloroanilino*-6-β-*diethylaminoethylaminoquinoline* (XIII, R = $CH_2 \cdot CH_2 \cdot NEt_2$) in good yield, but failed with 6-*amino*-4-p-*chloroanilinoquinoline* and with 8-*amino*-4-p-*chloroanilino*-6-*methoxyquinoline*, although higher temperatures and longer periods of heating were used in these attempts. Similarly, no product was obtained by heating δ-diethylamino-α-methylbutyl chloride and 6-amino-2-*p*-chloroanilinoquinoline in alcoholic solution.

The preparation of compounds with an arylamino-group in the benzene ring of the quinoline nucleus presents difficulties, and for the synthesis of compounds of types (XV and XVI; R = dialkylaminoalkyl, R′ = Cl), the reactions of ethyl ethoxymethylenemalonate with

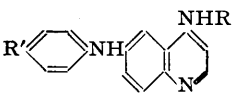

(XII.)


(XIII.)


(XIV.)


(XVI.)

(XV.)



4-chloro-4′-aminodiphenylamine and 4-chloro-2′-aminodiphenylamine were indicated. The preparation of 4-chloro-4′-aminodiphenylamine from nitrosobenzene and *p*-chloronitrosobenzene, as described in B.P. 338,240, was abandoned because of poor yields. 4-Chloro-2′-nitrodiphenylamine was prepared from *p*-chloroaniline and *o*-chloronitrobenzene, and subsequently reduced to 4-chloro-2′-aminodiphenylamine, by a modification of the method of Wilberg (*Ber.*, 1902, **35**, 957). The analogous preparation of 4-*chloro*-4′-*nitrodiphenylamine* by heating *p*-chloroaniline with *p*-chloronitrobenzene in the presence of anhydrous potassium carbonate required a temperature of at least 250°, and gave only a poor yield. The attempted preparation of this compound by heating *p*-chloroiodobenzene with *p*-nitroaniline in the presence of potassium carbonate, copper bronze, and potassium iodide gave 4 : 4′-*dichloro*-4″-*nitrotriphenylamine*. This was not altogether unexpected, since Mann and Porter (*J.*, 1947, 914) found preferential formation of the triphenylamine in a similar reaction, and they overcame this difficulty by the use of the acetyl derivative in place of the free base. When the *p*-nitroaniline in the above experiment was replaced by *p*-nitroacetanilide, however, the acetyl group was eliminated and the triphenylamine obtained as before. Although the reduction of 4-chloro-2′-nitrodiphenylamine with stannous chloride and hydrochloric acid, as described by Wilberg (*loc. cit.*), gave 4-chloro-2′-aminodiphenylamine in good yield, the attempted reduction of 4-chloro-4′-nitrodiphenylamine under the same conditions gave a product from which only *p*-chloroaniline was isolated. In the absence of a satisfactory method for the preparation of 4-chloro-4′-aminodiphenylamine, *p*-aminodiphenylamine was used for the preparation of a 6-arylaminoquinoline of type (XV) (R = dialkylaminoalkyl; R′ = H).

4-Chloro-2′-aminodiphenylamine and *p*-aminodiphenylamine, by warming with ethyl ethoxymethylenemalonate followed by cyclisation in boiling diphenyl ether and subsequent hydrolysis, gave 8-p-*chloroanilino*-4-*hydroxyquinoline*-3-*carboxylic acid* and 6-*anilino*-4-*hydroxyquinoline*-3-*carboxylic acid* respectively. The latter was decarboxylated above its melting point (255°) to 6-*anilino*-4-*hydroxyquinoline*. The hydroxyl group was replaced directly by the β-diethylaminoethylamino-group by interaction with β-diethylaminoethylamine, which gave 6-*anilino*-4-β-*diethylaminoethylaminoquinoline* (XV) (R = $CH_2 \cdot CH_2 \cdot NEt_2$; R′ = H). No product soluble in dilute acids was obtained by heating 6-anilino-4-hydroxyquinoline with δ-diethylamino-α-methylbutylamine. 8-*p*-Chloroanilino-4-hydroxyquinoline-3-carboxylic acid melted with decomposition at 310°, but was not decarboxylated by being heated either alone or in liquid paraffin.

Experimental.

Preparation of Chloronitroquinolines.

2-Chloro-5-nitro- and 2-Chloro-8-nitro-quinoline.—2-Chloroquinoline, prepared as described by Friedländer and Ostermaier (*Ber.*, 1882, **15**, 332) from 2-hydroxyquinoline obtained by the method of Tschitschibabin (*Ber.*, 1923, **56**, 1879), was nitrated as described by Fischer and Guthmann (*J. pr. Chem.*, 1916, **93**, 383). The mixed chloronitroquinolines (58·7 g., m. p. 104—125°), obtained in 80% yield after one recrystallisation from alcohol, gave on crystallisation twice from benzene (850 c.c. and 300 c.c.), crude 2-chloro-8-nitroquinoline (16·6 g., m. p. 140—148°), which was used without further purification for the preparation of 8-nitro-2-*p*-chloroanilinoquinoline. The mother-liquor from the first recrystallisation from benzene was evaporated to dryness, and gave a mixture (36·0 g.) enriched in 2-chloro-5-nitroquinoline, which was not further purified but used directly for the preparation of 5-nitro-2-*p*-chloroanilinoquinoline. Pure specimens of 2-chloro-5-nitroquinoline, m. p. 132—133°, and 2-chloro-8-nitroquinoline, m. p. 149—151°, were isolated from the original mixture of isomerides by repeated recrystallisation from benzene and alcohol and by distillation in superheated steam respectively.

2-Chloro-6-nitroquinoline.—6-Nitro-2-hydroxyquinoline was prepared by a modification of the method of Friedländer and Lazarus (*Annalen*, 1885, **229**, 245). A mixture of nitric acid (20 g., *d* 1·42) and concentrated sulphuric acid (200 g.) was added with stirring to a solution of 2-hydroxyquinoline (30 g.) in concentrated sulphuric acid (200 g.), the temperature being kept below 10°. The mixture was poured on ice, and the precipitate filtered off, washed, and dried. Recrystallisation from glacial acetic acid (800 c.c.) gave 6-nitro-2-hydroxyquinoline (34·7 g.), m. p. 277°. A mixture of 6-nitro-2-hydroxyquinoline (25 g.), phosphorus pentachloride (50 g.), and phosphorus oxychloride (200 g.) was heated under reflux for 2 hours, cooled, and poured on ice. The precipitate was filtered off, washed, and dried; recrystallisation from acetone (1 l.) gave 2-chloro-6-nitroquinoline (14·5 g.), m. p. 225—228° (cf. Bachman and Cooper, *J. Org. Chem.*, 1944, **9**, 302).

4-Chloro-6-nitroquinoline and 8-nitro-4-hydroxy-6-methoxyquinoline.—These compounds were prepared as described by Riegel *et al.* (*loc. cit.*), the former in 8% overall yield, m. p. 144—145°; the latter, obtained in 22% overall yield, m. p. 205—212°, was converted into 4-chloro-8-nitro-6-methoxyquinoline immediately before condensation with *p*-chloroaniline, as described below.

Preparation of p-*Chloroanilinoquinolines.*

2-p-*Chloroanilinoquinoline.*—A mixture of 2-chloroquinoline (4·4 g.) and *p*-chloroaniline (3·4 g.) was heated to 250° for a few minutes. The product was dissolved in hydrochloric acid, precipitated by the addition of aqueous sodium hydroxide, filtered off, washed, dried and recrystallised twice from alcohol. 2-p-*Chloroanilinoquinoline* (4·5 g.) was obtained in white scales, m. p. 144·5—145·5° (Found: C, 70·6; H, 4·4. $C_{15}H_{11}N_2Cl$ requires C, 70·7; H, 4·4%). The *picrate* separated in yellow needles from alcohol, m. p. 214—217° (Found: C, 52·4; H, 3·1. $C_{15}H_{11}N_2Cl,C_6H_3O_7N_3$ requires C, 52·1; H, 2·9%).

8-*Nitro*-2-p-*chloroanilinoquinoline.*—A mixture of crude 2-chloro-8-nitroquinoline, m. p. 140—148° (12·0 g.), prepared as described above, and *p*-chloroaniline (7·4 g.) was heated in an oil-bath until it became solid and a thermometer in it registered 180°. After cooling, the mass was boiled with sodium carbonate solution until completely disintegrated, collected, washed, dried, and recrystallised from xylene (400 c.c.). 8-*Nitro*-2-p-*chloroanilinoquinoline* (13·8 g.) was obtained in light brown needles, m. p. 206—208° (Found: C, 59·7; H, 3·4; N, 13·6; Cl, 12·1. $C_{15}H_{10}O_2N_3Cl$ requires C, 60·1; H, 3·4; N, 14·0; Cl, 11·8%). The m. p. was not depressed on admixture with a specimen prepared in the same manner from pure 2-chloro-8-nitroquinoline. The *acetyl* derivative separated from alcohol in pale yellow rhombohedra, m. p. 124·5—125·5° (Found: C, 59·8; H, 3·7. $C_{17}H_{12}O_3N_3Cl$ requires C, 59·7; H, 3·5%). The *picrate* formed short stout yellow-brown needles from acetone, m. p. 220—223° (Found: C, 47·5; H, 2·6. $C_{15}H_{10}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 47·7; H, 2·5%).

5-*Nitro*-2-p-*chloroanilinoquinoline.*—The solid (36·0 g.), obtained by evaporation of the first benzene mother-liquor from the recrystallisation of the product of nitration of 2-chloroquinoline as described above, and *p*-chloroaniline (30·0 g.) were heated to 205—225° in an oil-bath for 1 hour. After cooling, the mass was dissolved in concentrated hydrochloric acid (4 l.), filtered from the dark blue by-product, diluted with an equal volume of water, and neutralised with aqueous ammonia. The precipitate was filtered off, washed, and dried. Two recrystallisations from glacial acetic acid (300 c.c. and 100 c.c.) gave 5-*nitro*-2-p-*chloroanilinoquinoline* (11·8 g.) as an orange-scarlet microcrystalline powder, m. p. 197·5—198·5° (Found: C, 60·1; H, 3·6; N, 14·1. $C_{15}H_{10}O_2N_3Cl$ requires C, 60·1; H, 3·4; N, 14·0%). The m. p. was not depressed on admixture with a specimen prepared in the same manner from pure 2-chloro-5-nitroquinoline. The *acetyl* derivative separated from alcohol in pale yellow rhombohedra, m. p. 158° (Found: C, 59·8; H, 3·7. $C_{17}H_{12}O_3N_3Cl$ requires C, 59·7; H, 3·5%). The *benzoyl* derivative formed white plates from alcohol, m. p. 182—183° (Found: C, 65·7; H, 3·6. $C_{22}H_{14}O_3N_3Cl$ requires C, 65·4; H, 3·5%). The *picrate* separated from acetone in small, bright yellow needles, m. p. 229·5—230·5° (Found: C, 47·6; H, 2·5. $C_{15}H_{10}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 47·7; H, 2·5%).

6-*Nitro*-2-p-*chloroanilinoquinoline.*—A solution of 2-chloro-6-nitroquinoline (22·4 g.) and *p*-chloroaniline (13·7 g.) in xylene (500 c.c.) was heated under reflux for 2 hours. The solid which had separated was filtered off, and the filtrate refluxed for a further 10 hours and again filtered. The two batches of hydrochloride were heated with aqueous sodium carbonate. The liberated 6-*nitro*-2-p-*chloroanilinoquinoline* was filtered off, washed, and dried (23·9 g.). Crystallisation, first from glacial acetic acid (300 c.c.) and then from toluene (650 c.c.), gave a scarlet amorphous powder (21 g.), m. p. 197·5—198·5° (Found: C, 60·2; H, 3·4; N, 14·1. $C_{15}H_{10}O_2N_3Cl$ requires C, 60·1; H, 3·4; N, 14·0%). The *acetyl* derivative separated from alcohol in pale yellow prisms, m. p. 145—146° (Found: C, 59·1; H, 3·8; $C_{17}H_{12}O_3N_3Cl$ requires C, 59·7; H, 3·5%). The *picrate* was obtained as a yellow microcrystalline powder, m. p. 265° (Found: C, 48·0; H, 2·7. $C_{15}H_{10}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 47·7; H, 2·5%).

6-*Nitro*-4-p-*chloroanilinoquinoline.*—A mixture of 4-chloro-6-nitroquinoline (2·5 g.) and *p*-chloroaniline (1·5 g.) was heated for 10 minutes over a flame. The product was dissolved in glacial acetic acid, diluted

with water, filtered from the dark impurity, and neutralised with sodium hydroxide. The precipitate was filtered off, washed, and dried. Recrystallisation from toluene (300 c.c.) gave 6-*nitro*-4-p-*chloroanilinoquinoline* (2·1 g.) as an orange-brown microcrystalline powder, m. p. 235—237° (Found : C, 60·3; H, 3·4; N, 14·1. $C_{15}H_{10}O_2N_3Cl$ requires C, 60·1; H, 3·4; N, 14·0%). The *picrate* separated from alcohol in bright yellow needles, m. p. 275—276° (Found : C, 47·9; H, 2·5. $C_{15}H_{10}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 47·7; H, 2·5%).

8-*Nitro*-4-p-*chloroanilino*-6-*methoxyquinoline*.—8-Nitro-4-hydroxy-6-methoxyquinoline (7·7 g.) and phosphorus oxychloride (30 c.c.) were heated under reflux for 30 minutes. The excess of phosphorus oxychloride was removed under reduced pressure on the water-bath, and the residue poured on ice. The mixture was made slightly alkaline with ammonia, and the crude 4-chloro-8-nitro-6-methoxyquinoline (7·0 g.) filtered off, washed, dried, and dissolved in xylene (30 c.c.). The solution was filtered, and a solution of *p*-chloroaniline (3·8 g.) in xylene (10 c.c.) added. The hydrochloride of the product began to separate almost immediately from the warm solution, which was then boiled under reflux for 20 minutes to complete the reaction. The solid was filtered off, washed with ether, and heated on the water-bath with aqueous ammonia. The liberated 8-*nitro*-4-p-*chloroanilino*-6-*methoxyquinoline* was filtered off, washed, and dried. Recrystallisation from alcohol (200 c.c.) gave yellow plates (2·8 g.), m. p. 221—222·5° (Found : C, 58·0; H, 3·7. $C_{16}H_{12}O_3N_3Cl$ requires C, 58·3; H, 3·6%). The *picrate* separated from alcohol in fine orange needles, m. p. 220—227° (Found : C, 47·8; H, 2·8. $C_{16}H_{12}O_3N_3Cl,C_6H_3O_7N_3$ requires C, 47·3; H, 2·7%).

Preparation of Amino-p-*chloroanilinoquinolines.*

8-*Amino*-2-p-*chloroanilinoquinoline*.—A filtered solution of stannous chloride (25 g.) in concentrated hydrochloric acid (25 c.c.) was added to a suspension of 8-nitro-2-*p*-chloroanilinoquinoline (5·0 g.) in glacial acetic acid (50 c.c.), and the mixture was left for 2 days in the cold. The crystalline stannichloride was collected and suspended in water (100 c.c.), and a solution of sodium hydroxide (125 g.) in water (200 c.c.) added. The liberated base was filtered off, washed with aqueous sodium hydroxide and then with water, and dried in the oven. A solution of the base in alcohol was saturated with dry hydrogen chloride; evaporation to dryness gave the hydrochloride, which was dissolved in water and the free base precipitated by addition of aqueous sodium carbonate, filtered off, washed, and dried. Recrystallisation from 75% aqueous alcohol (140 c.c.) gave 8-*amino*-2-p-*chloroanilinoquinoline* (3·0 g.) in shining pale grey plates, m. p. 169·5° (Found : C, 66·3; H, 4·4; N, 15·2. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·5; N, 15·6%).

5-*Amino*-2-p-*chloroanilinoquinoline*.—5-Nitro-2-*p*-chloroanilinoquinoline (5·0 g.) was suspended in glacial acetic acid (50 c.c.), and a filtered solution of stannous chloride (25 g.) in concentrated hydrochloric acid (25 c.c.) added. The mixture was heated for 1 hour on the water-bath and cooled overnight in the refrigerator. The stannichloride was filtered off and suspended in water (100 c.c.), and a solution of sodium hydroxide (125 g.) in water (200 c.c.) added. The liberated base was filtered off, washed with aqueous sodium hydroxide and then with water, and dried in the oven. Recrystallisation from xylene (100 c.c.) and then from alcohol gave 5-*amino*-2-p-*chloroanilinoquinoline* (3·25 g.) in shining pale grey plates, m. p. 184—186° (Found : C, 67·0; H, 4·4. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·5%).

6-*Amino*-2-p-*chloroanilinoquinoline*.—A solution of stannous chloride (30 g.) in concentrated hydrochloric acid (30 c.c.) was added to a solution of 6-nitro-2-*p*-chloroanilinoquinoline (10·0 g.) in glacial acetic acid (100 c.c.) on the water-bath. After 15 minutes the solution was diluted with water (1 l.) and heated to 80°, and a solution of sodium carbonate (120 g. anhydrous) in water (500 c.c.) added slowly with stirring. The precipitate was filtered off and warmed with a solution of sodium hydroxide (200 g.) in water (300 c.c.). The base was filtered off, washed with aqueous sodium hydroxide and then with water, and dried in the oven. The crude base was extracted with carbon tetrachloride (Soxhlet), and the extract evaporated to dryness. The residue was dissolved in alcohol (100 c.c.) and poured into hot water (1 l.). The precipitated base was filtered off, washed, and dried in the oven. Crystallisation from alcohol gave 6-*amino*-2-p-*chloroanilinoquinoline* (7·8 g.) in pale grey shining plates. Crystallisation from carbon tetrachloride gave yellow rhombohedra, m. p. 145·5—147·5° (Found : C, 66·0; H, 4·5. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·5%).

6-*Amino*-4-p-*chloroanilinoquinoline*.—To a solution of 6-nitro-4-*p*-chloroanilinoquinoline (2·1 g.) in glacial acetic acid (21 c.c.) was added a solution of stannous chloride (6·3 g.) in hydrochloric acid (6·3 c.c.), and the mixture was heated for 1 hour on the water-bath and cooled overnight in the refrigerator. The stannichloride was filtered off and suspended in water (20 c.c.), and a solution of sodium hydroxide (50 g.) in water (80 c.c.) was added. After 1 hour's heating on the water-bath, the liberated base was filtered off, washed with aqueous sodium hydroxide and with water, and dried. Recrystallisation from 60% alcohol (40 c.c.) (with charcoal) gave 6-*amino*-4-p-*chloroanilinoquinoline* (1·4 g.) in pale brown needles which lost water of crystallisation and melted over the range 90—100°. With very slow heating a m. p. of 187—190° is obtained (Found : C, 62·1; H, 5·3; loss at 100° in a vacuum, 6·7. $C_{15}H_{12}N_3Cl,H_2O$ requires C, 62·6; H, 5·3; H_2O, 6·3%).

8-*Amino*-4-p-*chloroanilino*-6-*methoxyquinoline*.—A solution of stannous chloride (8·4 g.) in concentrated hydrochloric acid (8·4 c.c.) was added to a solution of 8-nitro-4-*p*-chloroanilino-6-methoxyquinoline (2·8 g.) in glacial acetic acid (28 c.c.) and the mixture was left overnight in the refrigerator. The stannichloride was filtered off and suspended in water (25 c.c.), and a solution of sodium hydroxide (50 g.) in water (80 c.c.) added. After 30 minutes' heating on the water-bath, the liberated base was filtered off, washed with aqueous sodium hydroxide and with water, and dried in the oven. Crystallisation from alcohol gave 8-*amino*-4-p-*chloroanilino*-6-*methoxyquinoline* (2·1 g.) in small green-yellow needles, m. p. 174·5—175·5° (Found : C, 60·3; H, 5·3. $C_{16}H_{14}ON_3Cl,H_2O$ requires C, 60·4; H, 5·0%).

Preparation of Arylaminodialkylaminoalkylaminoquinolines.

2-p-*Chloroanilino*-8-*β-diethylaminoethylaminoquinoline*.—8-Amino-2-*p*-chloroanilinoquinoline (4·8 g.) and diethylaminoethyl chloride (2·4 g.) in xylene (120 c.c.) were heated on the water-bath for 24 hours,

cooled, and extracted with 80 c.c. of 2·0N- and two 40 c.c. amounts of 1·0N-hydrochloric acid. The combined acid extracts were made strongly alkaline by the addition of potassium hydroxide (60 g.), and extracted twice with ether (60 c.c.). The combined ether extracts were dried (KOH), filtered, and saturated with dry hydrogen chloride. The precipitated 2-p-*chloroanilino*-8-*β*-*diethylaminoethylamino*-*quinoline hydrochloride* (5·0 g.) was filtered off, washed with a little dry ether, and dried in a vacuum; it was obtained as a bright yellow crystalline deliquescent solid. The *picrate* separated from alcohol in small bright yellow needles, m. p. 150·5—154·5° (Found: C, 47·6; H, 3·7; N, 16·3; Cl, 4·3. $C_{21}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·75; N, 16·9; Cl, 4·3%). The *tartrate*, prepared by the addition of a slight excess of an alcoholic solution of tartaric acid to an ethereal solution of the base, was obtained as a yellow crystalline solid, readily soluble in water but only slightly hygroscopic (Found: C, 52·9; H, 6·5. $C_{21}H_{25}N_4Cl,C_4H_6O_6,3H_2O$ requires C, 52·4; H, 6·5%).

2-p-*Chloroanilino*-5-*β*-*diethylaminoethylaminoquinoline*.—5-Amino-2-*p*-chloroanilinoquinoline (5·5 g.) and diethylaminoethyl chloride (2·7 g.) in xylene (100 c.c.) were heated on the water-bath for 24 hours, cooled, and extracted with dilute hydrochloric acid (200 c.c. of 2·0N acid in 4 portions). The combined acid extracts were made alkaline with potassium hydroxide, which precipitated a black tar. This was repeatedly shaken with 200 c.c. quantities of ether, and the combined extracts were dried (KOH), filtered, and saturated with dry hydrogen chloride. 2-p-*Chloroanilino*-5-*β*-*diethylaminoethylamino*-*quinoline hydrochloride* (6·6 g.) separated as a bright yellow crystalline deliquescent solid, which was purified by conversion into the free base and reprecipitation as hydrochloride. The *picrate* separated from alcohol in small yellow-brown flat prisms, which melted irregularly at about 200° (Found: C, 47·0; H, 4·1; N, 17·1; Cl, 3·9. $C_{21}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·75; N, 16·9; Cl, 4·3%). The *oxalate* was obtained as a yellow amorphous powder which darkened at 96°, and decomposed above this temperature or on being kept at room temperature for several months (Found: C, 55·6; H, 5·9; N, 11·0; Cl, 7·6. $C_{21}H_{25}N_4Cl,C_2H_2O_4,2H_2O$ requires: C, 55·8; H, 5·9; N, 11·4; Cl, 7·2%).

2-p-*Chloroanilino*-6-*β*-*diethylaminoethylaminoquinoline*.—6-Amino-2-*p*-chloroanilinoquinoline (4·1 g.) and diethylaminoethyl chloride hydrochloride (2·6 g.) in alcohol (100 c.c.) were heated under reflux on the water-bath for 3 hours. The greater part of the alcohol was removed under reduced pressure on the water-bath, and addition of dry ether (200 c.c.) precipitated 2-*p*-chloroanilino-6-*β*-diethylaminoethylaminoquinoline hydrochloride. This was filtered off, washed with ether and dried in a vacuum over phosphoric oxide. It was purified by conversion into the base and reprecipitation with dry hydrogen chloride as a bright yellow crystalline deliquescent solid (5·4 g.). The *picrate* separated from alcohol in clusters of orange crystals, m. p. (slow heating) 188—192° (Found: C, 47·3; H, 4·0. $C_{21}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·75%). The *oxalate* was obtained as a yellow powder, m. p. 183° (decomp.) (Found: C, 55·3; H, 5·7. $C_{21}H_{25}N_4Cl,C_2H_2O_4,2H_2O$ requires C, 55·8; H, 5·9%).

4-Chloro-4′-aminodiphenylamine was prepared in 14% yield as describe in B.P. 338,240, and 4-chloro-2′-aminodiphenylamine was obtained by a modification of the method of Wilberg (*loc. cit.*). A mixture of *o*-chloronitrobenzene (40·0 g.), *p*-chloroaniline (32·5 g.), and anhydrous potassium carbonate (35·0 g.) was heated under reflux in an oil-bath at 190—225° for 3 days. Concentrated hydrochloric acid (75 c.c.) was then added and the mixture was distilled with steam to remove unchanged reactants. The residual solid was filtered off, washed, dried, and extracted with ether (Soxhlet). Evaporation of the extract gave 4-chloro-2′-nitrodiphenylamine in red needles which were recrystallised from alcohol (400 c.c.) with charcoal (24·3 g.; m. p. 145·5°). Reduction, as described by Wilberg (*loc. cit.*), gave 4-chloro-2′-aminodiphenylamine (m. p. 115—118°) in 75% yield.

4-*Chloro*-4′-*nitrodiphenylamine*.—A mixture of *p*-chloronitrobenzene (100 g.), *p*-chloroaniline (80 g.), and anhydrous potassium carbonate (90 g.) was heated under reflux on a metal-bath at 255° for 3 days, cooled, and distilled with steam to remove unchanged reactants. Concentrated hydrochloric acid (100 c.c.) was added, and the solid filtered off, washed, dried, and extracted with ether (Soxhlet). The extract was evaporated to about 200 c.c., cooled, and filtered. The residue was washed with a little ether and extracted with alcohol (Soxhlet). The 4-*chloro*-4′-*nitrodiphenylamine*, which crystallised from the extract, was filtered off and recrystallised from alcohol (1400 c.c.); it was obtained in pale brown shining plates (10·3 g.), m. p. 186—186·5° (Found: C, 57·9; H, 3·1. $C_{12}H_9O_2N_2Cl$ requires C, 57·9; H, 3·1%).

4 : 4′-*Dichloro*-4″-*nitrotriphenylamine*.—(*a*) A mixture of *p*-nitroaniline (12·1 g.), *p*-chloroiodobenzene (30 g.), anhydrous potassium carbonate (10 g.), copper bronze (0·2 g.), and potassium iodide (0·1 g.) was heated under reflux in an oil-bath for 3½ hours. When cold, the mixture was extracted with alcohol (Soxhlet), and the solid which separated from the extract was filtered off and dissolved in alcohol (1500 c.c.). Addition of water precipitated 4 : 4′-*dichloro*-4″-*nitrotriphenylamine*, which after crystallisation 6 times from alcohol had m. p. 218—223° (1·0 g.) (Found: C, 59·7; H, 3·5. $C_{18}H_{12}O_2N_2Cl_2$ requires C, 60·2; H, 3·3%). (*b*) A mixture of *p*-nitroacetanilide (2·6 g.), *p*-chloroiodobenzene (17 g.), anhydrous potassium carbonate (1·5 g.), copper bronze (0·1 g.), and potassium iodide (0·05 g.) was heated under reflux (oil-bath at 240°) for 1¼ hours. The mixture after cooling was distilled with steam, and the residue was recrystallised thrice from alcohol. 4 : 4′-Dichloro-4″-nitrotriphenylamine (0·5 g.) was obtained in clusters of fairly large golden-yellow angular plates, m. p. 219·5—222·5°, not depressed on admixture with the specimen prepared by method (*a*) (Found: C, 59·65; H, 3·45%).

Reduction of 4-*Chloro*-4′-*nitrodiphenylamine*.—4-Chloro-4′-nitrodiphenylamine (4·8 g.), stannous chloride (17·7 g.), and concentrated hydrochloric acid (20 c.c.) were heated on the water-bath for 1 hour and cooled in the refrigerator. The stannichloride was filtered off and suspended in a solution of sodium hydroxide (40 g.) in water (100 c.c.). The solid was filtered off, washed with aqueous sodium hydroxide and then with water, and dried in a vacuum. The product was extracted with carbon tetrachloride and evaporated to dryness, and the residue extracted with light petroleum (b. p. 60—80°) (300 c.c.). Evaporation to about 80 c.c. deposited large octahedral crystals (1·0 g.), which after several recrystallisations from light petroleum (b. p. 40—60°) had m. p. 70—71°, depressed on admixture with an authentic specimen of 4-chloro-4′-aminodiphenylamine, prepared as described above, but not on admixture with *p*-chloroaniline (Found: C, 56·4; H, 4·9. Calc. for C_6H_6NCl: C, 56·6; H, 4·7%).

6-*Anilino*-4-*hydroxyquinoline*.—*p*-Aminodiphenylamine (25·8 g.) and ethyl ethoxymethylenemalonate

(31·8 g.) were heated on the water-bath for 20 minutes. The crude product (m. p. 111—116°) was melted and added dropwise to refluxing diphenyl ether (150 g.) during 10 minutes. Refluxing was continued for a further 5 minutes. When the mixture was cold, light petroleum (b. p. 60—80°; 200 c.c.) was added and the ethyl 6-anilino-4-hydroxyquinoline-3-carboxylate filtered off, washed, and dried in the oven. The ester which was obtained as a cream-coloured powder, m. p. 255° (decomp.), was hydrolysed by boiling under reflux for 1 hour with a solution of sodium hydroxide (30 g.) in 25% alcohol (400 c.c.). Neutralisation with dilute hydrochloric acid precipitated 6-anilino-4-hydroxyquinoline-3-carboxylic acid, which was filtered off, washed, and dried in the oven, being so obtained as a white powder, m. p. 255° (decomp.) (25·2 g.). It was decarboxylated by being heated in a oil-bath at 275° for 30 minutes. After cooling, the residue was dissolved in β-ethoxyethanol (100 c.c.), and the solution filtered and diluted with water (700 c.c.). *6-Anilino-4-hydroxyquinoline* (8·6 g.) separated on cooling in pale yellow-brown needles, m. p. 191—192° (Found: C, 70·8; H, 5·8. $C_{15}H_{12}ON_2,H_2O$ requires C, 70·8; H, 5·5%). The water is lost in the range 140—160°, and care is necessary to avoid a false m. p.

4-Chloro-6-anilinoquinoline.—6-Anilino-4-hydroxyquinoline (0·8 g.) and phosphorus oxychloride (5 c.c.) were heated under reflux for 1 hour. The mixture was cooled, poured on ice, and neutralised with sodium carbonate. The solid was filtered off, washed, and dried; crystallisation from benzene and then from light petroleum (b. p. 80—100°) gave *4-chloro-6-anilinoquinoline* (0·5 g.) in sheaves of stout yellow needles, m. p. 147—148° (Found: C, 70·6; H, 4·4. $C_{15}H_{11}N_2Cl$ requires C, 70·7; H, 4·3%).

6-Anilino-4-β-diethylaminoethylaminoquinoline.—6-Anilino-4-hydroxyquinoline monohydrate (4·9 g.) was heated for 10 minutes in an oil-bath at 210°, after which β-diethylaminoethylamine (6·0 g.) and 1 crystal of potassium iodide were added. The mixture was heated under reflux (oil-bath at 175°) for 72 hours. When cold, the mixture was dissolved in alcohol (100 c.c.), and a solution of picric acid (5 g.) in alcohol (50 c.c.) was added. After standing overnight in the refrigerator, the picrate which separated was filtered off, washed, dried, and heated on the water-bath with 15% aqueous potassium hydroxide. The liberated base was filtered off, washed, and dried. Crystallisation from benzene (20 c.c.) gave *6-anilino-4-β-diethylaminoethylaminoquinoline* (1·5 g.) in yellow-brown irregular crystals, m. p. 170·5—172·5° (Found: C, 74·6; H, 7·7; N, 16·7. $C_{21}H_{26}N_4$ requires C, 75·4; H, 7·8; N, 16·7%). The *picrate* separated from *cyclo*hexanone–alcohol in small orange needles, m. p. 201·5—207° (Found: C, 50·2; H, 4·2. $C_{21}H_{26}N_4,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·0%). The *hydrochloride* crystallised from acetone–water in fine pale yellow needles, m. p. 170·5—172·5° (Found: C, 56·1; H, 7·15. $C_{21}H_{26}N_4,2HCl,2H_2O$ requires C, 56·9; H, 7·2%).

Ethyl 8-p-*Chloroanilino-4-hydroxyquinoline-3-carboxylate.*—4-Chloro-2′-aminodiphenylamine (20·0 g.) and ethyl ethoxymethylenemalonate (20·0 g.) were heated on the water-bath for 3½ hours. The product, m. p. 119—131°, was added in small portions to a refluxing mixture of diphenyl (60 g.) and diphenyl ether (140 g.). The addition took 10 minutes, and refluxing was continued for a further 20 minutes. After cooling, light petroleum (b. p. 40—60°) (1 l.) was added, and the precipitated *ethyl* 8-p-*chloroanilino-4-hydroxyquinoline-3-carboxylate* filtered off, washed, dried, and recrystallised from pyridine (300 c.c.). The ester (17·9 g.) was obtained in minute pale cream needles, m. p. 236—244° (Found: C, 63·4; H, 4·4. $C_{18}H_{15}O_3N_2Cl$ requires C, 63·1; H, 4·4%). Hydrolysis of the ester by boiling under reflux for 1 hour with aqueous or aqueous-alcoholic sodium hydroxide, filtering, and neutralising with dilute hydrochloric acid gave 8-p-*chloroanilino-4-hydroxyquinoline-3-carboxylic acid* in almost quantitative yield as an orange-brown powder, m. p. 310° (decomp.), which can be recrystallised with difficulty from pyridine or pyridine–alcohol (Found: C, 61·5; H, 4·1. $C_{16}H_{11}O_3N_2Cl$ requires C, 61·0; H, 3·5%). Attempts to decarboxylate this acid by heating it either alone or in liquid paraffin were unsuccessful.

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