319. *Attempts to find New Antimalarials. Part XXX. The Synthesis of Derivatives of Quinolino(4′ : 3′-2 : 3)quinoline.*

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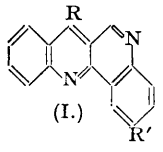
4-Anilinoquinoline-3-carboxylic acid and its derivatives are cyclized in concentrated sulphuric acid to the corresponding 4-hydroxyquinolino-(4′ : 3′-2 : 3)quinolines (I; R = OH), and with phosphorus oxychloride and pentachloride yield the analogous 4-chloroquinolino(4′ : 3′-2 : 3)quinolines (I; R = Cl). The halogen atom in the 4-position in these bases is stable to alkali but readily hydrolysed in the presence of acid and is replaced by the dialkylaminoalkylamino-group under conditions similar to those used for the isomeric 5- chloropyridoacridines which the quinolinoquinolines closely resemble.

Quinolino(4′ : 3′-2 : 3)quinoline (I; R = R′ = H) was first prepared by Clemo and Perkin (*J.*, 1924, **125**, 1608) who condensed 4-keto-1 : 2 : 3 : 4-tetrahydroquinoline with isatin and isolated the decarboxylated product, 1′ : 2′-dihydroquinolino(4′ : 3′-2 : 3)quinoline. This compound on distillation over lead oxide lost two atoms of hydrogen. Mann (*Nature*, 1949, **164**, 785; *J.*, 1949, 2816) has recently carried out similar reactions using 4-keto-1-phenyl-1 : 2 : 3 : 4-tetrahydroquinoline instead of 4-keto-1 : 2 : 3 : 4-tetrahydroquinoline and so obtained 1′ : 2′-dihydro-1′-phenylquinolino(4′ : 3′-2 : 3)quinoline, the salts of which are highly coloured, apparently owing to electromeric effects in the anion.



(I.)

In view of the considerable antimalarial activity of certain derivatives of pyridino(4′ : 3′-2 : 3)acridine carrying a basic side-chain in the 5-position it was considered desirable to synthesise analogous derivatives of quinolino(4′ : 3′-2 : 3)quinoline. An attempt was first made to prepare 4-chloroquinoline-3-carboxylic acid as it was thought that

this, by condensation with aniline, would readily yield 4-anilinoquinoline-3-carboxylic acid which could then be cyclized with the formation of 4-chloroquinolino(4′ : 3′-2 : 3)quinoline (I; R = Cl, R′ = H), a compound in which the chlorine atom, as in the corresponding 5-chloroacridine, should be readily replaceable by appropriate basic side chains.

Ethyl 4-hydroxyquinoline-3-carboxylate was easily converted into ethyl 4-chloroquinoline-3-carboxylate but hydrolysis of the ester group invariably resulted in the removal of chlorine with the formation of 4-hydroxyquinoline-3-carboxylic acid and so far we have been unable to prepare 4-chloroquinoline-3-carboxylic acid from the 4-hydroxy-acid. Ethyl 4-anilinoquinoline-3-carboxylate was however obtained by condensing ethyl 4-chloroquinoline-3-carboxylate with aniline followed by hydrolysis of the ester. The acid, which could not be easily recrystallised because of its tendency to form gels, yielded 4-anilinoquinoline on decarboxylation, and its identity was thus confirmed. On treatment with sulphuric acid at 100° 4-anilinoquinoline-3-carboxylic acid cyclized to give 4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline, whilst with phosphorus oxychloride it yielded 4-chloroquinolino(4′ : 3′-2 : 3)quinoline. The chlorine atom in this compound is readily split off by acids with formation of the 4-hydroxy-derivative, but the compound is stable to alkali and can be recrystallised unchanged from aqueous alcohol.

The 4-chloroquinolinoquinoline and its derivatives closely resemble 5-chloroacridine; in particular they are stable to alkali but are converted into the 4-hydroxyquinolinoquinolines in the presence of acid. The 4-chloroquinolinoquinolines are comparatively more stable to a hot solution of aqueous alcohol, but like 5-chloroacridines tend to give poor analytical data, indicating the presence of traces of the corresponding 4-hydroxy-compounds.

Attempts to prepare 4-chloro-6-methoxyquinoline-3-carboxylic acid from the 4-hydroxy-6-methoxy-acid or by hydrolysis from ethyl 4-chloro-6-methoxyquinoline-3-carboxylate failed, the chlorine atom being very readily hydrolysed as in the case of the corresponding compound without the methoxy-group. On the other hand, crude 4 : 6-dichloroquinoline-3-carboxylic acid was obtained from 6-chloro-4-hydroxyquinoline-3-carboxylic acid by treatment with phosphorus oxychloride and pentachloride. The presence of the chlorine atom in the 6-position evidently increases the stability of that in position 4; similar effects in the quinoline series have been observed by Drake *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1208). 4-Anilino-6-methoxyquinoline-3-carboxylic acid was obtained by condensing ethyl 4-chloro-6-methoxyquinoline-3-carboxylate with aniline and hydrolysing the product. 4 : 6-Dichloroquinoline-3-carboxylic acid condensed readily with aniline to yield 4-anilino-6-chloroquinoline-3-carboxylic acid. These two derivatives of 4-anilinoquinoline-3-carboxylic acid, when treated with warm sulphuric acid, yielded respectively 4-hydroxy-6′-methoxy- and 6′-chloro-4-hydroxy-quinolino(4′ : 3′-2 : 3)quinoline (I; R = OH, R′ = OMe and R = OH, R′ = Cl), and on treatment with phosphorus oxychloride they gave respectively 4-chloro-6′-methoxy- and 4 : 6′-dichloro-quinolinoquinoline.

These two 4-chloroquinolinoquinolines and also 4-chloroquinolino(4′ : 3′-2 : 3)quinoline itself could also be prepared from the corresponding 4-hydroxyquinolinoquinolines by refluxing them with phosphorus oxychloride containing phosphorus pentachloride. The yield in this reaction was usually poor but it was increased if a small quantity of hexadecyltrimethylammonium bromide ("Cetavlon") was added to the mixture before it was refluxed. For example, in the conversion of 4-hydroxy-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline to the 4-chloro-6′-methoxy-compound, the yield improved from 31% to 47% when "Cetavlon" was added. The mechanism whereby "Cetavlon" effects this improvement is not known, but reference may be made to its advantageous action in the preparation of 3-chloro-2-naphthoic acid from 3-hydroxy-2-naphthoic acid (Cairns and Kermack, *J.*, 1950, 1322) and to the advantageous action of the addition of surface-active agents in the preparation of anilides from 3-hydroxy-2-naphthoic acid in the presence of phosphorus pentachloride (see U.S.P. 2,394,279/1946).

4-Chloroquinolinoquinoline and its analogues react with alkylaminoalkylamines in the presence of phenol. In this way 4-(2-diethylaminoethylamino)quinolino(4′ : 3′-2 : 3)quinoline and 4-(4-diethylamino-1-methylbutylamino)-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline have been prepared.

These quinolinoquinoline derivatives carrying a basic side chain form yellow solids which readily dissolve in dilute acid to give yellow solutions with green fluorescence, and in general resemble the isomeric pyridoacridines. When analysed these bases gave satisfactory carbon and hydrogen values but micro-Dumas determinations of nitrogen gave results 1—3% below the theoretical values. When however the temperature of the combustion tube was raised to 900°, nitrogen figures within 0·5% of the theoretical result were obtained. This experience is similar to that reported by Braucone and Fulmon (*Analyt. Chem.*, 1949, **21**, 1147).

Experimental.

(M. p.s are uncorrected.)

Ethyl 4-Chloroquinoline-3-carboxylate.—Ethyl 4-hydroxyquinoline-3-carboxylate (5·4 g.) was refluxed with phosphorus pentachloride (5·2 g.) and phosphorus oxychloride (10 c.c.) for 2 hours. The cold solution was poured on crushed ice, decolorized (charcoal), and basified with dilute sodium hydroxide. *Ethyl 4-chloroquinoline-3-carboxylate* crystallised from light petroleum (b. p. 40—60°) in large white prisms, m. p. 37° (Found : C, 61·1; H, 3·9; N, 5·6. $C_{12}H_{10}O_2NCl$ requires C, 61·15; H, 4·2; N, 5·9%).

Ethyl 4-Anilinoquinoline-3-carboxylate.—Ethyl 4-chloroquinoline-3-carboxylate (2·3 g.) and aniline (0·9 g.) reacted almost immediately with evolution of heat when mixed thoroughly at room temperature, the product setting to a hard golden gum. Dissolution of this in water and basification with ammonia solution yielded *ethyl 4-anilinoquinoline-3-carboxylate*, which crystallised from ethanol in short yellow prisms, m. p. 99—100° (Found : C, 74·0; H, 5·5; N, 9·6. $C_{18}H_{16}O_2N_2$ requires C, 73·7; H, 5·5; N, 9·9%).

4-Anilinoquinoline-3-carboxylic Acid.—4-Anilinoquinoline-3-carboxylate was hydrolysed for 1 hour with 5% ethanolic sodium hydroxide; subsequent neutralization with dilute acetic acid yielded *4-anilinoquinoline-3-carboxylic acid* as a soapy gelatinous precipitate, m. p. 260—265° (Found : N, 11·0. $C_{16}H_{12}O_2N_2$ requires N, 10·6%). The product on being heated at its melting point was decarboxylated and yielded 4-anilinoquinoline, m. p. 196—198° (Ephraim, *Ber.*, 1893, **26**, 2229, gives m. p. 198°).

4-Hydroxyquinolino(4′ : 3′-2 : 3)quinoline.—4-Anilinoquinoline-3-carboxylic acid (0·5 g.) was heated at 95° with concentrated sulphuric acid (5 c.c.) for 30 minutes. A marked fluorescence developed which intensified as the heating continued. The cooled solution was poured on ice and basified with ammonia solution, yielding *4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline.* Recrystallised from ethanol, this formed long slender white fibres, which turned yellow on being dried. When these were moistened with water, the yellow colour disappeared and the colourless compound was regenerated. This had m. p. >360° (marked decomp.) (Found : C, 73·7; H, 4·2; N, 10·0. $C_{16}H_{10}ON_2$,0·75H_2O requires C, 74·0; H, 4·4; N, 10·7%).

4-Chloroquinolino(4′ : 3′-2 : 3)quinoline.—4-Anilinoquinoline-3-carboxylic acid (1 g.) was refluxed with phosphorus oxychloride (5 c.c.) for 2 hours. The excess of phosphorus oxychloride was distilled off under reduced pressure at 80°, and the residual yellow powder, dried as far as possible at the pump, was triturated with cold 20% sodium hydroxide solution. The brownish-red solid was filtered off, washed with water, and dried in a vacuum desiccator (KOH). When the product was digested with hot benzene in the presence of a pellet of potassium hydroxide, some 4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline remained undissolved; the *4-chloroquinoline(4′ : 3′-2 : 3)quinoline*, m. p. 210—215°, crystallised from the benzene solution on cooling. It recrystallised from dry toluene in pale yellow cubes, m. p. 210° (Found : C, 73·2; H, 3·2; N, 10·2. $C_{16}H_9N_2Cl$ requires C, 72·6; H, 3·4; N, 10·6%). This compound was also prepared by refluxing 4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline with phosphorus oxychloride and pentachloride for 6 hours.

Ethyl 4-Chloro-6-methoxyquinoline-3-carboxylate.—Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (15·5 g.) when refluxed with phosphorus oxychloride (20 c.c.) and pentachloride (13 g.) yielded *ethyl 4-chloro-6-methoxyquinoline-3-carboxylate*; this, when crystallised from light petroleum (b. p. 80—100°), had m. p. 84—86° (Found : N, 5·4. $C_{13}H_{12}O_3NCl$ requires N, 5·3%).

Ethyl 4-Anilino-6-methoxyquinoline-3-carboxylate.—Ethyl 4-chloro-6-methoxyquinoline-3-carboxylate (4·3 g.) and aniline (1·6 g.) were allowed to react at room temperature. *Ethyl 4-anilino-6-methoxyquinoline-3-carboxylate* was obtained as a white powder by the addition of ammonia solution to the hot aqueous solution of the resulting hydrochloride; recrystallised from ethanol it formed prisms, m. p. 101° (Found : N, 8·5. $C_{19}H_{18}O_3N_2$ requires N, 8·7%).

4-Anilino-6-methoxyquinoline-3-carboxylic Acid.—Ethyl 4-anilino-6-methoxyquinoline-3-carboxylate (20 g.) was hydrolysed by refluxing it with 5% ethanolic sodium hydroxide (100 c.c.) for 2 hours. When the product was precipitated by dilute acid it was obtained as a gelatinous compound which could not be crystallised from any of the ordinary solvents. *4-Anilino-6-methoxyquinoline-3-carboxylic acid* was purified by dissolving it in dilute sodium carbonate solution and reprecipitating the acid with dilute acetic acid. It had m. p. 264° (frothing) (Found : C, 65·1; H, 4·9; N, 9·2. $C_{17}H_{14}O_3N_2$,H_2O requires C, 65·3; H, 5·1; N, 9·0%).

4-Hydroxy-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline.—4-Anilino-6-methoxyquinoline-3-carboxylic acid (0·5 g.) when heated in concentrated sulphuric acid (5 c.c.) for 30 minutes yielded *4-hydroxy-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline*, which was isolated after dilution and precipitation with ammonia solution; it had m. p. 350° (marked decomp.) (Found : C, 74·0; H, 4·5; N, 9·7. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·7; N, 9·4%).

4-Chloro-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline.—4-Anilino-6-methoxyquinoline-3-carboxylic acid (1 g.) was heated in phosphorus oxychloride (30 c.c.) for 4 hours, and the product isolated as described for 4-chloroquinolino(4′ : 3′-2 : 3)quinoline. *4-Chloro-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline* crystallised from toluene in long shining yellow needles, m. p. 177—178° (Found : C, 66·9, 67·1; H, 3·7, 4·3; N, 8·6, 8·5. $C_{17}H_{11}ON_2Cl$,0·5H_2O requires C, 67·2; H, 3·95; N, 9·2%). This compound was also prepared by the action of phosphorus oxychloride and phosphorus pentachloride on 4-hydroxy-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline. The addition of " Cetavlon " (0·1 g.) to the reaction mixture increased the yield from 34% to 47%.

4-Anilino-6-chloroquinoline-3-carboxylic Acid.—6-Chloro-4-hydroxyquinoline-3-carboxylic acid (5 g.) was refluxed with phosphorus pentachloride (5·2 g.) and phosphorus oxychloride (15 c.c.) for 5 hours. When cold, the solution was poured on ice, and the resultant precipitate collected and dried in a vacuum over potassium hydroxide; it had m. p. 280—282° [the mixed m. p. with 6-chloro-4-hydroxyquinoline-3-

carboxylic acid (m. p. 278—279°) was 274°]. The crude dichloro-acid was used for the next stage in the synthesis as attempts to purify it resulted in loss of chlorine.

Crude 4 : 6-dichloroquinoline-3-carboxylic acid (8 g.) and aniline (2·3 g.) were mixed and warmed in a water-bath whereupon a reaction took place and the product set to a gum. *6-Chloro-4-anilinoquinoline-3-carboxylic acid* could not be obtained crystalline; it softened at 230° and had m. p. 260—262° (Found : N, 9·1. $C_{16}H_{11}O_2N_2Cl$ requires N, 9·4%).

6′-Chloro-4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline.—4-Anilino-6-chloroquinoline-3-carboxylic acid was cyclized in concentrated sulphuric acid at 100°, giving *6′-chloro-4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline*. The product, white needles (from ethanol), melted at >360° (Found : N, 10·0. $C_{16}H_9ON_2Cl$ requires N, 10·0%).

4 : 6′-Dichloroquinolino(4′ : 3′-2 : 3)quinoline.—4-Anilino-6-chloroquinoline-3-carboxylic acid (5 g.) was refluxed for 7 hours with phosphorus pentachloride (3 g.) and phosphorus oxychloride (20 c.c.) containing " Cetavlon " (0·1 g.). The product was isolated as described for the 4-chloro-compound. *4 : 6′-Dichloroquinolino(4′ : 3′-2 : 3)quinoline* crystallised from toluene as long white glistening fibres, m. p. 238° (Found : C, 63·4; H, 2·5; N, 9·4. $C_{16}H_8N_2Cl_2,0{\cdot}25H_2O$ requires C, 63·3; H, 2·8; N, 9·2%). This compound was also prepared by the action of phosphorus oxychloride on 6′-chloro-4-hydroxyquinolino(4′ : 3′-2 : 3)quinoline.

4-(2-Diethylaminoethylamino)quinolino(4′ : 3′-2 : 3)quinoline.—Freshly distilled phenol (5 g.) was heated in a vacuum on a steam-bath, and after 2 hours 2-diethylaminoethylamine (0·46 g.) was added, and the contents of the flask kept at 100° under vacuum for a further 2 hours. Dry 4-chloroquinolino-(4′ : 3′-2 : 3)quinoline (0·5 g.) was introduced, and the mixture heated at 100° under reflux. After 4 hours the cooled solution was poured into 2N-sodium hydroxide solution (30 c.c.), and the oily suspension extracted immediately with ether. The base was further purified by extraction of the ethereal solution with N-acetic acid, precipitation with ammonia solution, and re-extraction with ether. The ethereal solution was dried (K_2CO_3) and the ether removed. *4-(2-Diethylaminoethylamino)quinolino(4′ : 3′-2 : 3)quinoline* was crystallised from light petroleum (b. p. 80—100°); it formed rod-shaped crystals, m. p. 80—82° (Found : C, 76·65; H, 6·6; N, 15·9. $C_{22}H_{24}N_4$ requires C, 76·7; H, 6·9; N, 16·3%).

4-(4-Diethylamino-1-methylbutylamino)-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline.—A mixture of phenol (3 g.) and 2-amino-5-diethylaminopentane (1·5 g.) was dried under vacuum at 100° for 1 hour. Dry 4-chloro-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline (1 g.) was added, the dark-red solution heated under reflux at 100° for 4 hours, and the product worked up as described in the previous experiment. *4-(4-Diethylamino-1-methylbutylamino)-6′-methoxyquinolino(4′ : 3′-2 : 3)quinoline* crystallised from light petroleum (b. p. 60—80°) in long yellow prisms, m. p. 98—100° (Found : C, 75·2; H, 7·4; N, 13·4. $C_{26}H_{32}ON_4$ requires C, 75·0; H, 7·7; N, 13·5%).

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