FUSED HETEROCYCLICS

PART III. SYNTHESIS OF QUINOLINO-(2′:3′:3:4)-QUINOLINE[1]

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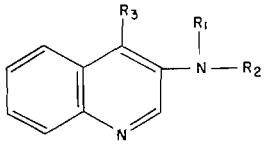
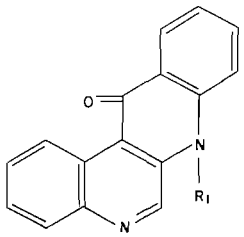
ABSTRACT

Quinolino-(2′:3′:3:4)-quinoline has been synthesized from 3-aminoquinoline-4-carboxylic acid via 4′-hydroxyquinolino-(2′:3′:3:4)-quinoline.

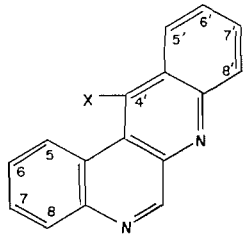
Quinolinoquinolines containing fused pyridine rings were of interest in connection with the structure of calycanine (1). In Part II of this series (2) the synthesis of quinolino-(2:3:3′:2′)-quinoline was reported. The synthesis of an angular isomer, quinolino-(2′:3′:3:4)-quinoline, is now described.



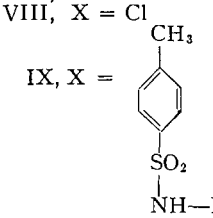
I, $R_1 = R_2 = H$; $R_3 = COOH$
II, $R_1 = Ph$; $R_2 = H$; $R_3 = COOH$
III, $R_1 = R_2 = Ph$; $R_3 = COOH$
IV, $R_1 = Ph$; $R_2 = R_3 = H$
V, $R_1 = R_2 = Ph$; $R_3 = H$



VII, $R_1 = Ph$



VI, X = OH
VIII, X = Cl



IX, X =

X, X = H

Although the base itself (X) has not been synthesized previously, 4′-hydroxy derivatives with substituents in the 2-, 6′-, 7′-, and 8′-positions have been prepared by the cyclization of appropriately substituted 3-arylaminoquinoline-4-carboxylic acids (3, 4, and 5). This method, in its essentials, was followed for the synthesis of 4′-hydroxyquinolino-(2′:3′:3:4)-quinoline.

The preparation of 3-phenylaminoquinoline-4-carboxylic acid (II) was carried out by the extension of the arylation reaction described in Part II (2). When 3-aminoquinoline-4-carboxylic acid (I) (6) was treated with iodobenzene and copper catalyst, a mixture of 3-phenylamino- and 3-(diphenylamino)-quinoline-4-carboxylic acids (II and III respectively) was obtained. As in the case of the corresponding quinaldine acid (2), the monosubstituted acid could not be obtained exclusively. The acids were separated by fractional crystallization and decarboxylated to the corresponding bases 3-phenylamino- and 3-(diphenylamino)-quinolines (IV and V), which were characterized as their picrates.

The mixture of acids obtained in the arylation reaction was cyclized with phosphoryl

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chloride, and the intermediate chloro derivatives hydrolyzed to give 4′-hydroxyquinolino-(2′:3′:3:4)-quinoline (VI) and 4′-keto-1′-phenyldihydroquinolino-(2′:3′:3:4)-quinoline (VII). The cyclized products were separated readily as they had markedly different solubilities in organic solvents. The 4′-hydroxy derivative (VI) gave a typical acridone-like fluorescence in presence of alkali (7) and was characterized as its picrate; whereas the 4′-keto compound was non-fluorescent and did not give any crystalline salts.

The reduction of the 4′-hydroxy derivative to the unsubstituted quinolinoquinoline with zinc dust did not prove successful. However, by using the method of Albert and Royer (8) for the conversion of acridone into acridine, the desired compound (X) was obtained. The 4′-hydroxy derivative (VI) was refluxed with phosphoryl chloride to give the 4′-chloro compound (VII) which was sensitive to hydrolysis with acid, but could be stored satisfactorily over potassium hydroxide *in vacuo*. It was characterized as the picrate. On treatment of the chloro derivative with *p*-toluenesulphonylhydrazide (8) in chloroform, the 4′-*p*-tosylhydrazidoquinolino-(2′:3′:3:4)-quinoline (IX) was obtained as the hydrochloride. Attempts to prepare the free base from its hydrochloride were unsuccessful and led to considerable decomposition. It was found that the reaction of the chloro derivative with *p*-tosylhydrazide was slower than in the case of the acridine derivative (8). The 4′-hydrazido hydrochloride was treated with 1 *N* sodium hydroxide in ethylene glycol to give a mixture of the 4′-hydroxy derivative (VI) and the desired quinolino-(2′:3′:3:4)-quinoline (X) which were readily separated by chromatography over alumina. The quinolinoquinoline crystallized from methanol in cream-colored needles m.p. 179°–180° C. Its ultraviolet absorption spectrum is recorded in Fig. 1.

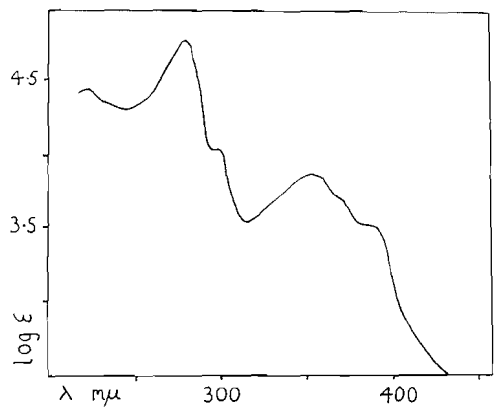

FIG. 1. Ultraviolet absorption spectrum of quinolino-(2′:3′:3:4)-quinoline in methanol.

EXPERIMENTAL

All melting points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford.

3-Phenylaminoquinoline-4-carboxylic Acid (II)

3-Aminoquinoline-4-carboxylic acid (I, 6.35 g) (6), 10 g (7.35 ml) iodobenzene, 9 g anhydrous potassium carbonate, and 0.8 g copper catalyst (Naturkupfer C) were refluxed in a mixture of 20 ml benzyl alcohol and 40 ml cyclohexanol for 3 hours with strict exclusion of moisture. The reaction mixture was cooled, diluted with 50 ml water, and steam-distilled to remove the alcohols. The solution was filtered hot into dilute acetic acid and allowed to stand at room temperature for 6–8 hours. The orange precipitate (9.2 g, m.p. 224°–232° C, with decomposition) was dried, and crystallized from a 1:1 mixture

of chloroform–methanol. Lemon-yellow feathery needles of the 3-phenylamino acid (II), m.p. 243°–244° C (decomp.), were obtained after several crystallizations. Found: C, 72.1; H, 4.8; N, 10.9. Calc. for $C_{16}H_{12}N_2O_2$: C, 72.7; H, 4.5; N, 10.6%. The acid was sparingly soluble in water, benzene, ether, and alcohol. Its solutions in alkali were colorless.

3-Phenylaminoquinoline (IV)

The acid (II, 1.2 g) was heated at 250° C for 1 hour. The acid melted with decomposition and after the first few minutes, some of the base started to sublime into the air condenser attached to the flask. After decarboxylation was complete, the contents of the flask were allowed to cool and were extracted with methanolic hydrochloric acid. The acid solution was poured into an excess of aqueous potassium hydroxide, and the aqueous solution extracted with ether. Evaporation of the ether extract after charcoal treatment gave an oil (0.9 g), which solidified on refrigeration. Crystallization from dilute methanol gave the base (IV) as needles, m.p. 121°–123° C. Found: C, 81.9; H, 5.45; N, 12.4. Calc. for $C_{15}H_{12}N_2$: C, 81.8; H, 5.45; N, 12.4%. The base was very soluble in organic solvents and its solutions exhibited a strong blue fluorescence in ultraviolet light.

The *picrate* prepared in methanol gave orange needles, m.p. 189°–190° C with decomposition. Found: N, 15.4. Calc. for $C_{21}H_{15}N_5O_7$: N, 15.6%.

3-(Diphenylamino)-quinoline-4-carboxylic Acid (III)

A suspension of 1.5 g of 3-amino acid (I) in 25 ml benzyl alcohol was refluxed with 2.0 g anhydrous potassium carbonate, 0.2 g. Naturkupfer C and 2.3 g (1.7 ml) iodobenzene for 6 hours. The reaction was worked up as in the case of the 3-phenylamino acid (II) described above when 1.95 g of a bright yellow solid, m.p. 255°–264° C, was obtained. This was washed with acetone and crystallized from chloroform–methanol in stout yellow rods, m.p. 270°–272° C with decomposition. Found: C, 77.5; H, 4.8; N, 8.1. Calc. for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.8; N, 8.2%. The acid was sparingly soluble in most organic solvents but was readily soluble in aqueous alkali to give colorless solutions. It was insoluble in dilute mineral acids but dissolved in concentrated hydrochloric acid on prolonged boiling.

3-(Diphenylamino)-quinoline (V)

The acid (III, 1.5 g) was decarboxylated at 270° C for 1 hour. On working up the reaction as in the case of the 3-phenylamino compound (IV), an oil (1.0 g), solidifying on refrigeration was obtained (m.p. 155°–164° C with previous softening). Repeated crystallizations from dilute methanol or other organic solvents failed to raise the melting point and the base was therefore purified by sublimation at 180° C under reduced pressure (20 mm). Crystallization of the sublimate from dilute methanol gave colorless needles, m.p. 162°–164° C. Found: C, 84.7; H, 5.4; N, 9.7. Calc. for $C_{21}H_{16}N_2$: C, 85.1; H, 5.4; N, 9.4%. The base was very soluble in organic solvents to give yellowish solutions with a vivid blue fluorescence.

The *picrate* prepared from equimolecular quantities of the base and picric acid in benzene–methanol formed orange needles, m.p. 205°–206° C with decomposition. Found: C, 61.9; H, 3.7; N, 13.6. Calc. for $C_{27}H_{19}N_5O_7$: C, 61.7; H, 3.7; N, 13.3%.

4′-Hydroxyquinolino-(2′:3′:3:4)-quinoline (VI)

Five grams of the crude 3-phenylamino acid (II) were refluxed with 12.5 ml phosphoryl chloride under anhydrous conditions. A vigorous reaction set in at 60°–65° C and heating was interrupted till it was over. The refluxing was continued for 90 minutes the bath temperature being maintained at 110–120° C. Phosphoryl chloride was removed under

reduced pressure, care being taken that the bath temperature did not exceed 100° C. The dark residue, after removal of the acid chloride, was heated on the steam bath with 300 ml 1 *N* hydrochloric acid for 2 hours, filtered, and poured into excess ammonium hydroxide. After 16 hours at room temperature the dark solid was filtered, dried, and extracted with hot chloroform to remove the 4′-keto compound (vide infra) formed from the disubstituted acid (III). The residue was extracted with hot ethanol (charcoal) and the 4′-hydroxy derivative obtained by evaporation of the ethanol was crystallized from dilute acetic acid in yellow needles, m.p. 360° C. Found (sample dried at 100° C under 2 mm): C, 72.9; H, 4.6. Calc. for $C_{16}H_{10}N_2.H_2O$: C, 72.7; H, 4.5. Found (sample dried at 250° C under 0.5 mm): C, 74.9; H, 4.6. Calc. for $C_{16}H_{10}N_2O.H_2O$: C, 75.0; H, 4.3%. Attempts to remove the last 0.5 molecule of water of crystallization were unsuccessful even after repeated sublimation and extensive drying. The 4′-hydroxy compound was sparingly soluble in ether, benzene, and chloroform but readily so in ethanol and ethyl acetate. Its alcoholic solutions were non-fluorescent but gave a vivid green fluorescence in presence of a pellet of potassium hydroxide.

The *picrate* formed by refluxing (VI) with picric acid in ethanol for 4 hours gave needles, m.p. 255°–258° C. Found: C, 55.9; H, 3.1; N, 14.8. Calc. for $C_{22}H_{13}N_5O_8$: C, 55.6; H, 2.7; N, 14.8%.

4′-Keto-1′-phenyldihydroquinolino-(2′:3′:3:4)-quinoline (VII)

Diphenylamino acid (III, 0.8 g) was refluxed with 5 ml phosphoryl chloride and the reaction worked up as above. The 4′-keto derivative (VII) was obtained from the chloroform extract as a dark solid (0.6 g). Treatment with charcoal and crystallization from methanol gave pale yellow needles, m.p. 282°–284° C. Found: C, 81.8; H, 4.4; N, 8.7. Calc. for $C_{22}H_{14}N_2O$: C, 82.0; H, 4.4; N, 8.7%.

4′-Chloroquinolino-(2′:3′:3:4)-quinoline (VIII)

4′-Hydroxy compound (VI, 1.5 g) was refluxed with 20 ml phosphoryl chloride under anhydrous conditions for 6 hours. After removal of the acid chloride under reduced pressure, the orange-colored solid was added to a vigorously stirred 5% aqueous ammonium hydroxide containing crushed ice. The solution was kept alkaline to phenolphthalein by adding more ammonia if necessary. After 30 minutes the solution was centrifuged and the cream-colored solid dried in a vacuum desiccator over potassium hydroxide. Extraction of the dry solid with benzene containing a pellet of potassium hydroxide gave the 4′-chloro compound which crystallized from petroleum ether (b.p. 40°–60° C) in colorless prismatic needles, m.p. 191°–192° C. Found: C, 73.0; H, 3.8; Cl, 13.1. Calc. for $C_{16}H_9N_2Cl$: C, 72.6; H, 3.4; Cl, 13.4%.

The *picrate* formed in benzene gave orange needles, m.p. 209°–210° C with decomposition. Found: C, 54.0; H, 2.6. Calc. for $C_{22}H_{12}N_5O_7Cl$: C, 53.5; H, 2.4%.

4′-p-Tosylhydrazidoquinolino-(2′:3′:3:4)-quinoline Hydrochloride (IX)

The 4′-chloro compound (VIII, 0.18 g) was dissolved in the minimum quantity of chloroform and added to a saturated solution of 0.17 g *p*-tosylhydrazide (8) in the same solvent. After 48 hours at room temperature, the solution turned pale yellow but no solid separated. The chloroform was removed on the steam bath and fresh chloroform added to the reaction mixture which was left at room temperature for a further 72 hours. (It was found that a fast stream of hydrogen chloride when passed through the solution after the initial 48 hours gave the hydrochloride of (VIII) in one experiment.) After the completion of the reaction, the red solid was filtered from the chloroform, dried, and

crystallized from methanol containing a drop of hydrochloric acid in red needles which did not melt but decomposed at 320° C. Found: C, 61.5; H, 4.2. Calc. for $C_{23}H_{19}N_4SO_2Cl$: C, 61.3; H, 4.2%.

Quinolino-(2′:3′:3:4)-quinoline (X)

One half gram of (IX) was heated on the steam bath with 10 ml 1 *N* sodium hydroxide in ethylene glycol (4 g sodium hydroxide dissolved in a mixture of 70 ml ethylene glycol and 30 ml water) for 3 hours. The solution turned crimson and lumps of a precipitate were formed which were broken up from time to time with a glass rod. Evolution of gas began after the first few minutes and continued for 2 hours, when the solution became clear. It was then diluted with 20 ml water and refrigerated overnight. The flocculent precipitate that had separated was filtered after 24 hours, taken up in 1 *N* hydrochloric acid, and reprecipitated with ammonia. The base was taken up in ethyl acetate and chromatographed over alumina, when the quinolinoquinoline (X) separated as a strongly fluorescent band in ultraviolet light. Elution with ethyl acetate gave (X) which crystallized from methanol in needles, m.p. 179°–180° C. Found: C, 83.1; H, 4.5. Calc. for $C_{16}H_{10}N_2$: C, 83.5; H, 4.4%. The base was readily soluble in ethyl acetate, alcohol chloroform, and ether. It dissolved in mineral acids to give non-fluorescent solutions

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