NOTES

4-HYDROXYQUINALDINES IN THE MANNICH REACTION¹

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Many quinoline derivatives possess chemotherapeutic activity, but their usefulness may be interfered with by water insolubility. It was anticipated that introduction of a basic side chain would overcome the difficulty through hydrochloride formation. Quinaldine itself had been treated with formaldehyde and a primary or secondary amine hydrochloride to form 2-B-aminoethylquinoline derivatives (1). A German patent reported that treatment of 2-methyl-8-nitroquinoline with a primary amine hydrochloride gave a product having the basic side chain at the 2-position (2).

The same patent claims that, in the case of 4-hydroxyquinaldine, the reaction involves the methyl group at the 2-position (3). Price and Jackson carried out the reaction with 7-methoxy-4-hydroxyquinaldine, formaldehyde, and di-*n*-butylamine; they obtained the 3-dibutylaminomethyl derivative (4). Ghosh and Chandhuri treated 4-hydroxyquinaldine with diethylamine and formaldehyde and obtained 3-diethylaminomethyl-4-hydroxyquinaldine (5) (I), but they did not demonstrate its structure.

In the present work, 4-hydroxyquinaldine was treated with paraformaldehyde and diethylamine in 95% alcoholic solution at room temperature for 24 h. The product was assigned structure I, with the basic side chain attached to the 3-position. The methyl group at the 2-position remained intact, as shown by its condensation with p-dimethyl-aminobenzaldehyde in the presence of zinc chloride to give the carbostyryl derivative II. Also, hydrogenolysis of I with copper chromite catalyst gave 2,3-dimethyl-4-quinolinol (6) (III). The 4-hydroxyl group of I, in contrast to that of 4-hydroxyquinaldine, could be acetylated. When the product IV was treated with alkali, it hydrolyzed to regenerate I. Also, I, when condensed with chloroacetic acid, gave V.



I: R = OH, $R_1 = CH_2N(C_2H_5)_2$, $R_2 = CH_3$ II: R = OH, $R_1 = CH_2N(C_2H_5)_2$, $R_2 = CH=CHC_6H_5N(CH_3)_2$ III: R = OH, $R_1 = R_2 = CH_3$ IV: $R = OCOCH_3$, $R_1 = CH_2N(C_2H_5)_2$, $R_2 = CH_3$ V: $R = OCH_2COOH$, $R_1 = CH_2N(C_2H_5)_2 \cdot HCl$, $R_2 = CH_3$

When diethylamine hydrochloride was used in place of diethylamine, the product was the hydrochloride of I. When diethylamine was used in the presence of excess concentrated hydrochloric acid, the reaction failed to occur.

The Mannich reaction was carried out with 6- and 8-methyl-4-hydroxyquinaldine to give VI and VII, respectively. Upon hydrogenolysis, the corresponding 3-methyl derivatives VIII and IX were obtained. Both were identical with authentic samples prepared by condensation of α -methyl acetoacetic ester with p- and o-toluidine, respectively, followed by cyclization of the resulting crotonate derivatives.

¹Taken from the M.Sc. dissertation of M. Nasr, National Research Centre, Dokki, Cairo, 1965.

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EXPERIMENTAL

All melting points are uncorrected and were determined on a Kofler hot stage.

3-Diethylaminomethyl-4-hydroxyquinaldine (I)

A mixture of 1.6 g of paraformaldehyde (0.017 mole), 25 ml of 95% ethyl alcohol, and 20 ml (14.22 g, 0.194 mole) of diethylamine was refluxed until the paraformaldehyde had dissolved. To this solution was added 7.95 g (0.05 mole) of 4-hydroxyquinaldine (7) dissolved in the least amount of 95% ethanol; then the mixture was kept for 48 h at room temperature. White needles were formed. Recrystallization from alcohol gave 10.98 g (90% yield) of I, which decomposed at 348-350° (lit. (5) no melting until 300°).

Anal. Calcd. for C15H20ON2: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.60; H, 8.30; N, 11.36.

S-Diethylaminomethyl-4-hydroxyquinaldine Hydrochloride (Ia)

The foregoing procedure was applied, except that diethylamine was replaced by its hydrochloride. The reaction mixture was refluxed for 5 h. The solvent was then evaporated and the residue was recrystallized from aqueous alcohol to give a 95% yield of I*a*, m.p. 313–315°. Anal. Calcd. for C₁₅H₂₁ON₂Cl: N, 9.98; Cl, 12.65. Found: N, 9.65; Cl, 12.14.

When Ia was heated with 10% potassium hydroxide solution, I was recovered.

Condensation of I with p-Dimethylaminobenzaldehyde

A mixture of 2.44 g (0.01 mole) of I, 1.49 g (0.01 mole) of p-dimethylaminobenzaldehyde, and 0.5 g of zinc chloride was heated in an oil bath at 180 °C for 3 h. The reaction mixture was dissolved in alcohol. Upon addition of sodium hydroxide solution, a yellow substance was precipitated. Recrystallization from alcohol gave 2.6 g (70% yield) of 2-(p-dimethylaminostyryl)-3-diethylaminomethyl-4-quinolinol (II), m.p. 185-187°, which was soluble in alcohol but insoluble in water, ether, and petroleum ether.

Anal. Caled. for C24H29ON3: C, 76.59; H, 7.73; N, 11.20. Found: C, 76.44; H, 7.54; N, 11.12.

Hydrogenolysis of I

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A mixture of 7.32 g (0.03 mole) of J, 150 ml of absolute ethyl alcohol, and 5 g of copper chromite was placed in a bomb, hydrogen was added, and the mixture was shaken and heated gradually to 175° at an equilibrium pressure of 3 000 lb, for 4 h, until the calculated amount of hydrogen was consumed (0.045 mole). The bomb was allowed to cool to room temperature. The reaction mixture was filtered from the catalyst, concentrated, and cooled in ice. Precipitation by addition of ether and recrystallization from water gave 1.7 g (34% yield) of III, m.p. 319-320°. Its melting point was identical with that of an authentic sample of III and showed no depression upon admixture (lit. (6) m.p. 319-320°).

Acetvlation of I

A mixture of 1.55 g (0.012 mole) of I and 2 ml of acetic anhydride was heated in an oil bath at 180 °C for 3 h. The reaction mixture changed to a dark-red syrup. When this was poured into boiling water, a brown solid separated. This was filtered off, dried, and then recrystallized from absolute ethyl alcohol to give 1.5 g (85% yield) of 3-diethylaminomethyl-4-acetoxyquinaldine (IV), m.p. 314-316°, as yellow crystals insoluble in water, ether, petroleum ether, and chloroform, and soluble (with difficulty) in alcohol.

Anal. Caled. for C17H22O2N2: C, 71.30; H, 7.74; N, 9.79. Found: C, 71.15; H, 7.59; N, 9.61.

Acetvlation of III

The above procedure was applied to III, which was recovered unchanged (no depression in mixed melting point).

Attempt to Acetylate 4-Hydroxyquinaldine

The foregoing procedure was applied to 4-hydroxyquinaldine but the compound was recovered unchanged (no depression in melting point when mixed with starting material).

Hydrolysis of IV

A mixture of 0.15 (0.0006 mole) of IV, 0.2 g (0.0036 mole) of potassium hydroxide, and 5 ml of ethyl alcohol was refluxed on the water bath for 3 h, cooled, and poured into cold water. The precipitated solid was 3-diethylaminomethyl-4-hydroxyquinaldine (I), which decomposed at 348-350° (undepressed upon admixture with an authentic sample).

Reaction of I with Chloroacetic Acid

A mixture of 2.44 g (0.01 mole) of I and 0.945 g (0.01 mole) of chloroacetic acid was heated in an oil bath until solution was complete. The mixture was cooled and made alkaline with aqueous sodium hydroxide.

The yellow solid that separated was filtered off, dissolved in alcohol, and precipitated by a stream of hydrogen chloride to give 2.1 g (70% yield) of 3-diethylaminomethyl-4-carboxymethoxyquinaldine hydrochloride (V). It was recrystallized from absolute alcohol, and had m.p. 360-363°.

Anal. Calcd. for C17H23O3N2Cl: C, 60.26; H, 6.84; N, 8.27. Found: C, 60.12; H, 6.71: N, 8.41.

Attempted Reaction of Chloroacetic Acid with 4-Hydroxyquinaldine

The foregoing procedure was applied to 4-hydroxyquinaldine, but only unchanged starting material was obtained.

6-Methyl-3-diethylaminomethyl-4-hydroxyquinaldine (VI)

A mixture of 1.6 g (0.017 mole) of paraformaldehyde, 25 ml of 95% ethyl alcohol, and 20 ml (14.22 g, 0.194 mole) of diethylamine was refluxed on the water bath until the paraformaldehyde had dissolved, and then allowed to cool to room temperature. To this solution was added 8.65 g (0.05 mole) of 2,6-dimethyl-4quinolinol dissolved in the least amount of 95% ethanol; then the mixture was refluxed for 3 h and allowed to cool to room temperature. White needles insoluble in water and alkali but soluble in 5% hydrochloric acid were formed. Recrystallization from ethyl alcohol gave 11.52 g (90% yield) of VI, which decomposed at 320°.

Anal. Calcd. for C16H22ON2: C, 74.40; H, 8.58; N, 10.85. Found: C, 74.39; H, 8.47; N, 10.78.

Hydrogenolysis of VI

The hydrogenolysis of VI was effected in a manner similar to that used for the hydrogenolysis of I. The resulting reaction product was recrystallized from aqueous alcohol to give needles, m.p. 349-352°, easily soluble in alcohol and soluble (with difficulty) in water. The product showed no depression in the melting point upon admixture with an authentic sample of 3,6-dimethyl-4-hydroxyquinaldine (VIII) prepared by an alternative synthesis.

Anal. Caled. for C12H13ON: C, 77.01; H, 6.95; N, 7.49. Found: C, 76.87; H, 7.37; N, 7.25.

8-Methyl-S-diethylaminomethyl-4-hydroxyquinaldine (VII)

The foregoing procedure for VI was applied to 2,8-dimethyl-4-quinolinol. The reaction product was recrystallized from alcohol to give VII (90% yield), m.p. 338-340°, soluble in 5% hydrochloric acid and insoluble in water and alkali.

Anal. Calcd. for C16H22ON2: C, 74.40; H, 8.58; N, 10.85. Found: C, 74.39; H, 8.59; N, 10.64.

Hydrogenolysis of VII

The same procedure as described above for I was applied. The resulting reaction product was recrystallized from aqueous alcohol. The product melted at 325-327°. It showed no depression in the mixture melting point with 3,8-dimethyl-4-hydroxyquinaldine (IX).

Anal. Caled. for C12H13ON: C, 77.01; H, 6.95; N, 7.49. Found: C, 76.94; H, 7.10; N, 7.52.

3,6-Dimethyl-4-hydroxyquinaline (VIII)

A mixture of 10.7 g ($\overline{0.1}$ mole) of p-toluidine and 14.41 g (0.1 mole) of α -methylacetoacetate ester, to which was added two drops of concentrated hydrochloric acid, was kept at room temperature for 24 h. After separation of water, the residual p-toluidino- α -methylcrotonate was added dropwise to hot paraffin oil (150 ml) at 240°. The temperature was raised to 265°, and the mixture was then cooled. The white crystalline product was filtered off and washed with petroleum ether. It had m.p. 347°. Recrystallization from alcohol gave 12 g (64% yield) of VIII, m.p. 349-352°.

Anal. Caled. for C12H13ON: C, 77.01; H, 6.95; N, 7.49. Found: C, 76.95; H, 6.95; N, 7.54.

3,8-Dimethyl-4-hydroxyquinaldine (IX)

A mixture of 10.7 g (0.1 mole) of o-toluidinc and 14.41 g (0.1 mole) of α -methylacetoacetic ester was treated similarly as above, and the isolated product was recrystallized from alcohol to give 8.4 g (45% yield) of IX, m.p. 325-327°.

Anal. Caled. for C12H13ON: C, 77.01; H, 6.95; N, 7.49. Found: C, 76.82; H, 6.54; N, 7.61.

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