127. *Nitration of Derivatives of 4-Hydroxyquinaldine.*

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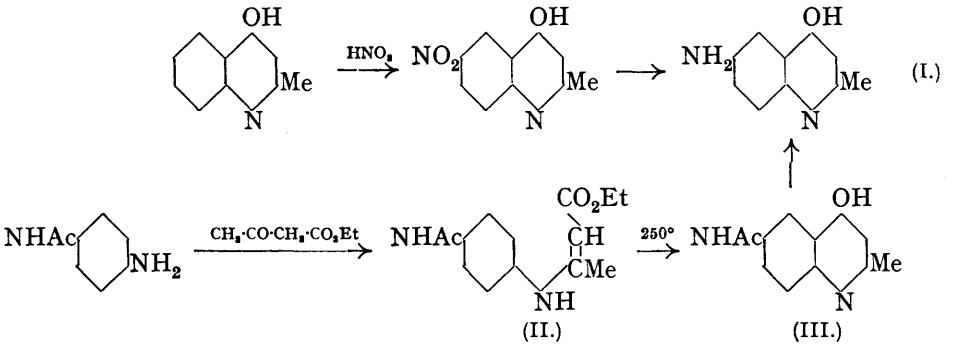
4-Hydroxyquinaldine and 4-hydroxy-2 : 3-dimethylquinoline on nitration both yield *mononitro*-derivatives, from which the corresponding *amines* are obtained on reduction. The latter have been synthesised from *p*-aminoacetanilide and ethyl acetoacetate or ethyl methylacetoacetate, from which it follows that the nitro-group enters the quinoline nucleus in the 6-position. Various derivatives of 6-nitro- and 6-acetamido-quinaldine are described.

IT has been shown by Balaban (J., 1930, 2349) that the nitration of 2-hydroxylepidine yields solely the 6-nitro-derivative. When 4-hydroxyquinaldine is nitrated, a homogeneous product is obtained, m. p. over 400°, which on reduction yields the corresponding amino-compound. Attempts made to establish the position of the amino-group in this compound by converting it into the corresponding chloro- or bromo-derivative by the Sandmeyer reaction, for comparison with 6-*chloro*- and 6-*bromo*-4-*hydroxy*-2-*methylquinoline* prepared by known methods from *p*-chloro- and *p*-bromo-aniline and ethyl acetoacetate through ethyl β-*p*-chlorophenylaminocrotonate and *ethyl* β-p-*bromophenylaminocrotonate*

respectively, did not yield crystalline products. The identity of the aminohydroxyquinaldine as the 6-amino-derivative (I) was finally established by its synthesis by the following alternative method. *p*-Aminoacetanilide readily reacted with ethyl acetoacetate,



in alcoholic solution containing a trace of hydrochloric acid, to yield *ethyl* β-p-*acetamidophenylaminocrotonate* (II), which, on being added to medicinal paraffin at 250°, was converted into 6-*acetamido*-4-*hydroxy*-2-*methylquinoline* (III); this on hydrolysis formed 6-*amino*-4-*hydroxy*-2-*methylquinoline* (I), identical in all respects with the amino-compound previously obtained. The two acetyl derivatives also were identical. It follows that 4-hydroxy-2-methylquinoline is nitrated in the 6-position.

Similar results were obtained with 4-hydroxy-2 : 3-dimethylquinoline, which, when nitrated, yielded a mononitro-derivative, reducible to a monoamino-derivative. The latter compound was identical with 6-*amino*-4-*hydroxy*-2 : 3-*dimethylquinoline* synthesised in the usual way from *p*-aminoacetanilide and ethyl methylacetoacetate through *ethyl* β-p-*acetamidophenylamino*-α-*methylcrotonate* and 6-*acetamido*-4-*hydroxy*-2 : 3-*dimethylquinoline*.

By the action of a mixture of phosphorus oxychloride and pentachloride on 6-acetamido-4-hydroxy-2-methylquinoline, 4-*chloro*-6-*acetamido*-2-*methylquinoline* was obtained, which on hydrolysis yielded 4-*chloro*-6-*amino*-2-*methylquinoline*. 4-Chloro-6-acetamido-2-methylquinoline reacted with piperidine, somewhat slowly on the water-bath, more rapidly under reflux, to form 6-*acetamido*-4-*piperidino*-2-*methylquinoline*, and with β-diethylaminoethylamine to form 4-β-*diethylaminoethylamino*-6-*acetamido*-2-*methylquinoline hydrochloride*.

The action of mixtures of phosphorus oxychloride and pentachloride on 6-*nitro*-4-*hydroxy*-2-*methylquinoline* yielded sometimes 4-*chloro*-6-*nitro*-2-*methylquinoline* and at others only amorphous products. 4-Chloro-6-nitro-2-methylquinoline yielded 6-*nitro*-4-*piperidino*-2-*methylquinoline* with piperidine and 6-*nitro*-4-β-*diethylaminoethylamino*-2-*methylquinoline* with β-diethylaminoethylamine.

Experimental.

Nitration of 4-*Hydroxy*-2-*methylquinoline*.—The solution obtained by stirring a mixture of nitric acid (*d* 1·42; 4·9 c.c.) and concentrated sulphuric acid (5 c.c.) into a solution of 4-hydroxy-2-methylquinoline (10·6 g.) in concentrated sulphuric acid (50 c.c.) at 0° was kept for 2 hours at room temperature and poured into ice-water. The crystalline *nitro*-compound which slowly separated was recrystallised from glacial acetic acid, forming yellow rods (8·5 g.), m. p. above 400° (Found: N, 13·5. $C_{10}H_8O_3N_2$ requires N, 13·7%), soluble in boiling dilute mineral acids, in cold dilute sodium hydroxide and sodium carbonate solutions and in aqueous ammonia, forming deep yellow solutions, very slightly soluble in hot alcohol, and slightly soluble in hot methyl alcohol, ligroin, and benzene.

6-*Amino*-4-*hydroxy*-2-*methylquinoline*.—The nitro-derivative (6·12 g.) was slowly added to a boiling solution of stannous chloride (20·34 g.) in concentrated hydrochloric acid (60 c.c.) and heated on the water-bath for 5 hours. The pale yellow solid which separated on cooling was collected and dissolved in water, tin removed with hydrogen sulphide, and the filtrate evaporated to small bulk. The hydrochloride (m. p. 300—305°), which separated in needles, was dissolved in water and basified with ammonia and the crystals separating were recrystallised

from boiling water, forming colourless, shimmering, rectangular plates (3·8 g.), m. p. 345°, after blackening at 320° (Found: N, 16·4. $C_{10}H_{10}ON_2$ requires N, 16·3%). The *base* was soluble in dilute acids, insoluble in sodium hydroxide solution, soluble in boiling alcohol, very slightly soluble in ligroin, chloroform, acetone and benzene, and insoluble in ether. The solution in alcohol had a strong blue-green fluorescence.

Acetylation.—The base (0·5 g.) and a large excess of acetic anhydride (3 c.c.) were warmed together on the water-bath under reflux for 4 hours. The white solid which separated on cooling was recrystallised from boiling water, forming small needles (0·35 g.), m. p. 365° after blackening at 330° (Found: N, 12·2. $C_{12}H_{12}O_2N_2,H_2O$ requires N, 12·0%). It was soluble in dilute acids, dilute sodium hydroxide and sodium carbonate solutions, boiling water, boiling alcohol and methyl alcohol, but insoluble in chloroform and ligroin.

Nitration of 4-Hydroxy-2 : 3-dimethylquinoline.—The base (11·6 g.) was dissolved in concentrated sulphuric acid (50 c.c.) and cooled to 0°, and a mixture of nitric acid (*d* 1·42; 4·5 c.c.) and concentrated sulphuric acid (5 c.c.) added. *6-Nitro-4-hydroxy-2 : 3-dimethylquinoline*, isolated as in the previous case and recrystallised from nitrobenzene, formed small greenish-yellow needles (7·8 g.), m. p. 380° (Found: N, 12·8. $C_{11}H_{10}O_3N_2$ requires N, 13·0%). The properties of this compound are very similar to those of 6-nitro-4-hydroxy-2-methylquinoline except that the solubility in alcohol and other organic solvents is markedly greater.

6-Amino-4-hydroxy-2 : 3-dimethylquinoline.—Reduction of the nitro-compound was effected as in the case of 6-nitro-4-hydroxy-2-methylquinoline. The hydrochloride of the amino-base, which separated in long, colourless prisms, m. p. 335°, was dissolved in water and neutralised with sodium carbonate solution. The *base* separated in crystals, which, recrystallised from boiling water, formed ball-shaped clusters of needles, m. p. 326°. Yield, 0·64 g. from 1 g. of the nitro-compound (Found: N, 15·2. $C_{11}H_{12}ON_2$ requires N, 14·9%). The properties of this base are very similar to those of 4-hydroxy-6-amino-2-methylquinoline.

6-Chloro-4-hydroxy-2-methylquinoline.—A mixture of *p*-chloroaniline (0·5 g.) and acetoacetic ester (0·5 g.) containing 0·02 c.c. of concentrated hydrochloric acid (cf. Thomson and Wilson, J., 1936, 856) was kept over sulphuric acid in an evacuated desiccator overnight. The dehydrated oily product, ethyl β-*p*-chlorophenylaminocrotonate, was slowly added to medicinal paraffin at 250°. After 5 minutes, the solid was separated from the cooled oil, washed with light petroleum, and recrystallised from methyl alcohol; it formed shimmering white plates (0·56 g.), m. p. 320—322° (Found: N, 7·3. $C_{10}H_8ONCl$ requires N, 7·2%), soluble in boiling dilute mineral acids, hot dilute sodium hydroxide solution, and methyl alcohol, but insoluble in sodium carbonate solution, alcohol, benzene and ligroin.

Ethyl β-p-*bromophenylaminocrotonate* (6·2 g.), similarly obtained from *p*-bromoaniline (5 g.), crystallised from light petroleum in feathery needles, m. p. 54° (Found: N, 5·0. $C_{12}H_{14}O_2NBr$ requires N, 4·9%), insoluble in alkalis, soluble in warm dilute mineral acids, ligroin, alcohol and methyl alcohol, and very soluble in benzene.

Heated in medicinal paraffin at 250° for 15 minutes, the ester (5 g.) was converted into *6-bromo-4-hydroxy-2-methylquinoline*, which crystallised from aqueous alcohol in sheaves of colourless needles (3·7 g.), m. p. 338° (Found: N, 6·0. $C_{10}H_8ONBr$ requires N, 5·9%), very similar in properties to 6-chloro-4-hydroxy-2-methylquinoline.

Ethyl β-p-*Acetamidophenylaminocrotonate.*—A solution of *p*-aminoacetanilide (7·5 g.) in the minimum amount of boiling alcohol was mixed with ethyl acetoacetate (6·5 g.) and concentrated hydrochloric acid (0·05 c.c.), heated on the water-bath for 15 minutes, and diluted with water. The precipitated *ester* crystallised from benzene in colourless needles (11·8 g.), m. p. 180° (Found: N, 11·0. $C_{14}H_{18}O_3N_2$ requires N, 10·7%), soluble in hot dilute mineral acids and in alcohol, insoluble in hot dilute alkali and light petroleum.

Heated in medicinal paraffin at 260°, the ester (1 g.) was converted into 6-acetamido-4-hydroxy-2-methylquinoline, which crystallised from alcohol in colourless plates (0·7 g.), m. p. 368° after blackening at 330° (Found: N, 13·2. Calc. for $C_{12}H_{12}O_2N_2$: N, 13·0%), identical with the acetylated 6-amino-4-hydroxy-2-methylquinoline already described.

Ethyl β-p-*acetamidophenylamino-α-methylcrotonate*, prepared from *p*-aminoacetanilide and ethyl methylacetoacetate in alcohol containing hydrochloric acid as in the case of ethyl β-*p*-acetamidophenylaminocrotonate, crystallised from aqueous alcohol in small, colourless plates, m. p. 169° (Found: N, 10·3. $C_{15}H_{20}O_3N_2$ requires N, 10·1%), soluble in hot dilute mineral acids, alcohol, benzene and acetone, slightly soluble in ligroin, and insoluble in alkali.

Heated in medicinal paraffin at 260°, the ester (1 g.) was converted into *6-acetamido-4-hydroxy-2 : 3-dimethylquinoline*, which crystallised from alcohol in colourless, small plates (0·63 g.), m. p. 385° after blackening at 350° (Found: N, 12·0. $C_{13}H_{14}O_2N_2$ requires N,

12·2%). This compound resembled 6-acetamido-4-hydroxy-2-methylquinoline in properties and on hydrolysis furnished 6-amino-4-hydroxy-2 : 3-dimethylquinoline identical with the base already described.

4-Chloro-6-nitro-2-methylquinoline.—6-Nitro-4-hydroxy-2-methylquinoline (6 g.) was refluxed with phosphorus oxychloride (8 c.c.) and phosphorus pentachloride (16·2 g.) for 1 hour at 120°. The purple solution, after cooling, was poured on ice, and the aqueous solution obtained was filtered and basified with sodium hydroxide. The white solid precipitate crystallised from alcohol in colourless needles (4·2 g.), m. p. 142° (Found : N, 12·5. $C_{10}H_7O_2N_2Cl$ requires N, 12·6%), insoluble in alkali, soluble in dilute mineral acids, alcohol, methyl alcohol and ligroin, and very soluble in benzene, acetone and ether.

6-Nitro-4-piperidino-2-methylquinoline.—4-Chloro-6-nitro-2-methylquinoline (0·3 g.) and piperidine (0·5 c.c.) were warmed on the water-bath for 1 hour. The solid which separated on cooling crystallised from aqueous alcohol in golden leaflets (0·28 g.), m. p. 145° (Found : N, 15·5. $C_{15}H_{17}O_2N_3$ requires N, 15·6%), insoluble in alkali, soluble in dilute acids, alcohol, methyl alcohol, ligroin and acetone, and very soluble in benzene.

6-Nitro-4-β-diethylaminoethylamino-2-methylquinoline. — 4-Chloro-6-nitro-2-methylquinoline (0·3 g.) and β-diethylaminoethylamine (0·5 c.c.) were refluxed together at 140° for 3 hours. On addition of water to the solution, after cooling, a bright yellow solid separated, which, recrystallised from aqueous alcohol, had m. p. 100—102°. Yield, 0·23 g. (Found : N, 16·7. $C_{16}H_{22}O_2N_4,2H_2O$ requires N, 16·6%). The *base* was insoluble in alkali, soluble in dilute acids, alcohol, methyl alcohol, benzene and ligroin, and very soluble in chloroform.

4-Chloro-6-bromo-2-methylquinoline.—6-Bromo-4-hydroxy-2-methylquinoline (0·34 g.), phosphorus oxychloride (4 c.c.), and phosphorus pentachloride (0·5 g.) were refluxed at 120° for 4 hours. The product was poured on ice, and the aqueous solution neutralised with sodium hydroxide. The white solid which separated crystallised from aqueous alcohol in long colourless needles (0·35 g.), m. p. 75° (Found : N, 5·3. $C_{10}H_7NClBr$ requires N, 5·5%), insoluble in alkali, soluble in dilute acids, alcohol, methyl alcohol, benzene and ligroin, and very soluble in acetone and chloroform.

4-Chloro-6-acetamido-2-methylquinoline.—6-Acetamido-4-hydroxy-2-methylquinoline (0·5 g.), phosphorus oxychloride (4 c.c.), and phosphorus pentachloride (0·5 g.) were refluxed at 120° for 1 hour, and the product worked up in the usual way. The white solid which separated on neutralisation with sodium hydroxide was recrystallised from benzene; m. p. 210°. Yield, 0·48 g. (Found : N, 11·8. $C_{12}H_{11}ON_2Cl$ requires N, 11·9%). It was soluble in dilute mineral acid, insoluble in dilute alkali solution, very soluble in alcohol, soluble in methyl alcohol and benzene, and slightly soluble in ligroin.

4-Chloro-6-amino-2-methylquinoline.—4-Chloro-6-acetamido-2-methylquinoline (0·3 g.) was refluxed with 1 c.c. of concentrated hydrochloric acid and 4 c.c. of water for 15 minutes. After cooling, the solution was neutralised with sodium hydroxide and the bright yellow solid precipitated was recrystallised from benzene; m. p. 145°. Yield, 0·18 g. (Found : N, 14·3. $C_{10}H_9N_2Cl$ requires N, 14·6%). It was soluble in dilute mineral acids, insoluble in dilute aqueous sodium hydroxide, sodium carbonate, and ammonia, very soluble in ethyl alcohol and methyl alcohol, soluble in benzene, and slightly soluble in ligroin.

6-Acetamido-4-piperidino-2-methylquinoline.—4-Chloro-6-acetamido-2-methylquinoline (0·2 g.) and piperidine (1 c.c.) were refluxed at 130° for 2 hours. Water was added to the solution after cooling, and the white solid obtained was crystallised by precipitating it with water from a filtered alcoholic solution; m. p. 87° (Found : N, 14·2; H_2O, 5·9. $C_{17}H_{21}ON_3,H_2O$ requires N, 14·0; H_2O, 6·0%). The *base* was insoluble in alkali, soluble in dilute acids, and boiling water, very soluble in alcohol, and slightly soluble in methyl alcohol.

4-β-Diethylaminoethylamino-6-acetamido-2-methylquinoline Hydrochloride.—4-Chloro-6-acetamido-2-methylquinoline (0·2 g.) and β-diethylaminoethylamine (1 c.c.) were refluxed at 140—150° for 4 hours. After removal of the excess of diethylaminoethylamine in a vacuum on the water-bath, a sticky brown oil remained, which solidified to a yellow solid when rubbed with acetone. It crystallised from alcohol–acetone in ball-shaped clusters of needles, m. p. 272° (Found : N, 15·6. $C_{18}H_{26}ON_4,HCl$ requires N, 16·0%). The *hydrochloride* was very soluble in water and alcohol, slightly soluble in ether, and insoluble in acetone, ligroin and benzene.

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