

## A STUDY OF HETEROCYCLIC QUINONES

## III. Synthesis and Properties of 8-Dialkylamino-4-hydroxy-2-methylquinoline 5,6-Quinones\*

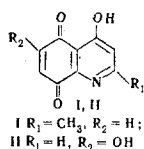
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By the oxidation of 4,6-dihydroxyquinaldine with oxygen in the presence of an equivalent amount of copper acetate and secondary amines, we have obtained 8-dialkylamino-4-hydroxy-2-methylquinoline 5,6-quinones, which have been saponified with alkali to form 4,6-dihydroxy-2-methylquinoline 5,8-quinones. The question of the role of the copper ions and the influence of tautomerism on the oxidation reaction is discussed. Some properties of the compounds obtained have been studied: reduction with hydrazine hydrate and phenylhydrazine and reaction with *o*-phenylenediamine. An assignment of the bands of the carbonyl absorption in the IR spectra of the quinones obtained has been made. By  $pK_a$  measurements it has been shown that the acidity of the hydroxyl hydrogen at  $C_4$  in the 4-hydroxyquinoline quinones is considerably higher than in 4-hydroxyquinoline.

Quinoline quinones substituted in positions 2, 3, and 4 have been studied very little. In particular, only two 5,8-quinone derivatives of 4-hydroxyquinoline have been reported in the literature: 4-hydroxy-2-methylquinoline 5,8-quinone (I) [1] and 4,6-dihydroxyquinoline 5,8-quinone (II) [2]. Both compounds were obtained comparatively recently by oxidation of the corresponding hydroquinones, which were synthesized by a fairly complex route. 4-Hydroxyquinoline 5,6-quinones have not previously been obtained.

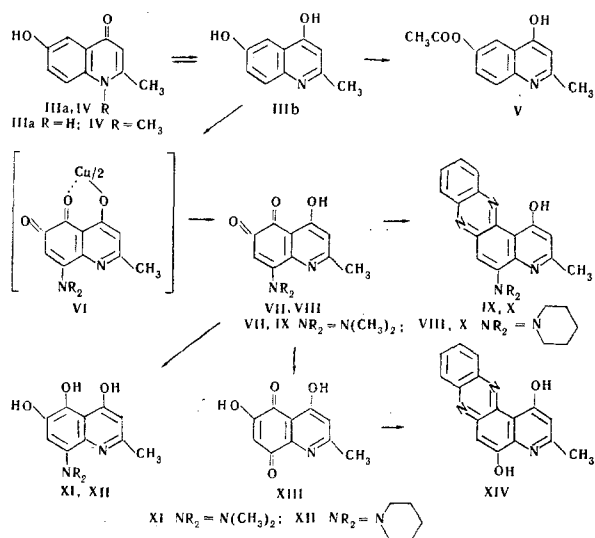


It appeared of interest to study the possibility of the direct oxidation of 4,6-dihydroxyquinolines into 8-dialkylamino-4-hydroxyquinoline 5,6-quinones by the method that we have developed for obtaining 8-dialkylaminoquinoline 5,6-quinones [3]. As the starting material we used 4,6-dihydroxyquinaldine (III), which was obtained by the demethylation of 4-hydroxy-6-methoxyquinaldine with sulfuric acid. Since the melting point of III differed from that given in the literature and this substance had previously been obtained by another method [4], the III was characterized additionally in the form of the acetate V.

When III was oxidized with oxygen in methanol in the presence of secondary amines and catalytic amounts of copper acetate, the reaction mixture rapidly became red because of the formation of a quinone. Only a small amount of oxygen was absorbed but the reaction rapidly ceased. This fact is easy to explain if one bears in mind that the quinone formed is capable of binding cop-

per in the form of a complex of the type of VI. In actual fact, when 0.5 mole of copper acetate was used in the reaction per mole of phenol, the reaction took place rapidly with the absorption of almost the calculated amount (1.5 mole) of oxygen. The idea of the formation by the hydroxyquinones VII-VIII of stable complexes with copper is also confirmed by the fact that, after the completion of the reaction, to isolate the quinones the reaction mixture must be acidified with a strong acid (for example, hydrochloric or oxalic acid), which destroys the complex. Acetic acid is unsuitable.

The phenol III, like other 4-hydroxyquinolines, is capable of existing in two tautomeric forms IIIa and IIIb. According to Albert and Phillips [5], for the unsubstituted 4-hydroxyquinoline in neutral aqueous solution the equilibrium is shifted strongly in the direction of the oxo form. In the presence of bases (piperidine, dimethylamine) the equilibrium must be shifted in the direction of the enolic form. Electronegative substituents apparently interfere with the oxidation of the substituted phenols to the corresponding quinones [6], and therefore we have put forward the hypothesis that III is oxidized in the enolic form IIIb. To confirm this, we synthesized 6-hydroxy-1,2-dimethylquinol-4-one (IV) [7], which exists as the pure oxo form. As was to be expected, this compound is not oxidized by oxygen in the presence of a copper-secondary amine complex.

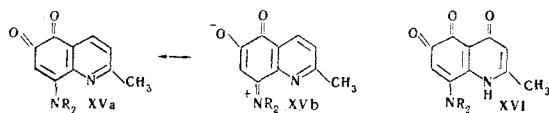


The hydroxyquinones VII and VIII differ from the compounds unsubstituted in position 4 (XVa) by their deeper coloration—they are dark brown crystalline

\*For part II, see [3].

substances. Like other quinoline 5,6-quinones, they give phenazines (IX, X) with *o*-phenylenediamine, and under the action of hydrazine or phenylhydrazine they are reduced to 4,5,6-trihydroxyquinolines (XI, XII). A comparison of the IR spectra of the hydroxyquinones VII and VIII with the spectra of the corresponding quinones unsubstituted in position 4 enables the bands of carbonyl absorption to be assigned. In the quinones

**XVa** ( $\text{NR}_2 = \text{N}(\text{CH}_3)_2$  and  $\text{N} \begin{array}{c} \diagup \\ \diagdown \end{array}$ ) there are two bands in the 1600–1700  $\text{cm}^{-1}$  region [3]—at about 1690 and 1620  $\text{cm}^{-1}$ . The 1690  $\text{cm}^{-1}$  band can be assigned to  $\text{C}_5=\text{O}$  and the 1620  $\text{cm}^{-1}$  band to  $\text{C}_6=\text{O}$ , since in the aminoquinones  $\nu_{\text{C}=\text{O}}$  is shifted in the long-wave direction because of the contribution of structure **XVb**.



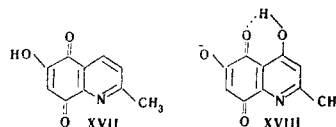
The 4-hydroxyquinones also have two bands in the 1600–1700  $\text{cm}^{-1}$  region: at 1650 and 1620  $\text{cm}^{-1}$  for VII and at 1650 and 1625  $\text{cm}^{-1}$  for VIII. The position of the band ascribed to  $\text{C}_6=\text{O}$  has scarcely changed, while the  $\text{C}_5=\text{O}$  band has shifted from 1690 to 1650  $\text{cm}^{-1}$ , which is explained by the formation of a hydrogen bond between the  $\text{C}_5=\text{O}$  carbonyl and the hydroxyl at  $\text{C}_4$ . Thus, there are reasons for considering that in the solid state the hydroxyquinones VII and VIII exist in the hydroxy form and not in the keto form XVI. This is confirmed by the absence from their IR spectra of bands in the 3300–3100  $\text{cm}^{-1}$  region ascribed to N—H stretching vibrations [8].

The carbonyl groups have a marked influence on the acidity of the hydroxyl hydrogen at  $\text{C}_4$ . The acidity constants of the quinones VII and VIII were determined by potentiometric titration with 0.001 M solutions (titration with a glass electrode using a LPU-01 pH meter). Because of hydrolysis of the quinones, the determination was carried out as fast as possible and the first three points, corresponding to 10, 20, and 30% neutralization, were taken for averaging. The quinone VII has  $\text{pK}_a$   $6.57 \pm 0.05$  (water, 20° C) and the quinone VIII  $\text{pK}_a$   $7.00 \pm 0.1$  (10% ethanol, 20° C). If these values are compared with the acidity of unsubstituted 4-hydroxyquinoline, which has  $\text{pK}_a$  11.25 [5], it can be seen that in VII and VIII the acidity has risen more than four orders of magnitude. As acids, the 4-hydroxyquinones VII and VIII are stronger than the nitrophenols ( $\text{pK}_a > 7.1$ ) and are comparable with hydrogen sulfide ( $\text{pK}_{a1}$  7.0) and carbonic acid ( $\text{pK}_{a1}$  6.4) [9].

The alkaline saponification of the hydroxyquinones VII and VIII led to 4,6-dihydroxy-2-methylquinoline 5,8-quinone (XIII), which, like the 6-hydroxyquinoline 5,8-quinones obtained previously [2, 3, 10], gives a phenazine (XIV) with *o*-phenylenediamine. The dihydroxyquinone XIII, which we obtained in the form of the monohydrate, differs from the dihydroxyquinone II synthesized by German workers only by the presence of a methyl group in position 2. A comparison of the maxima in the UV spectra of II [2] and XIII (see Experimental) and their phenazines shows that they are very

similar. The IR spectrum of XIII has two carbonyl maxima—at 1683 and 1630  $\text{cm}^{-1}$ . The 1683  $\text{cm}^{-1}$  band can be ascribed to  $\text{C}_8=\text{O}$  and the 1630  $\text{cm}^{-1}$  band, shifted in the long-wave direction because of the formation of a hydrogen bond, to  $\text{C}_5=\text{O}$ .

The dihydroxyquinone XIII behaves as a dibasic acid: potentiometric titration gave  $\text{pK}_{a1}$   $3.21 \pm 0.02$  and  $\text{pK}_{a2}$   $9.85 \pm 0.05$  (0.001 M solution, water, 20° C). As we have shown previously [3], the 6-hydroxy-2-methylquinoline 5,8-quinone unsubstituted in position 4 (XVII) has  $\text{pK}_a$  4.18. The increase in acidity due to the replacement of the hydrogen at  $\text{C}_4$  by an OH group can be explained by the formation of a chelate bond facilitating the detachment of the first proton [11]. In addition to this, the detachment of the second proton from the ion XVIII is obstructed and therefore  $\text{pK}_{a2}$  of the dihydroxyquinone XIII is 9.85, as compared with a value of 6.5–7 for the hydroxyquinones VII and VIII.



## EXPERIMENTAL

**4,6-Dihydroxyquinaldine (III).** A solution of 40 g (0.21 mole) of 6-methoxy-4-hydroxyquinaldine in a mixture of 112 ml of water and 200 ml of conc  $\text{H}_2\text{SO}_4$  was boiled for 5 hr, and then the reaction mixture was poured into 2 l of water and treated with 5 g of activated carbon, heated to 70–80° C, and filtered. The filtrate was made alkaline with 20% ammonia and cooled, and the precipitate of dihydroxyquinaldine was filtered off, washed with 200 ml of water, dried on the filter, and recrystallized with carbon from 150 ml of dimethylformamide. Yield 29.5 g (72.4%). Colorless crystals readily soluble in acetic acid and dimethylformamide, moderately soluble in methanol and ethanol, sparingly soluble in acetone, dioxane, ethyl acetate, and water, and insoluble in benzene, ether, and petroleum ether. Mp 309–311° C (decomp.). Found, %: C 62.18; H 5.81; N 7.62. Calculated for  $\text{C}_{10}\text{H}_9\text{NO}_2 \cdot \text{H}_2\text{O}$ , %: C 62.16; H 5.74; N 7.25.

**6-Acetoxy-4-hydroxyquinaldine (V).** A mixture of 1.0 g of III, 0.51 g of anhydrous potassium acetate, and 5 ml of acetic anhydride was boiled for 40 min, and then the reaction mixture was cooled, treated with 10 ml of water, and triturated to harden the precipitate. This was separated off, washed with water, and recrystallized from ethanol. Yield 0.9 g (80%). Colorless crystals, readily soluble in acetic acid, methanol, ethanol, moderately soluble in water, sparingly soluble in dioxane and acetone, and insoluble in benzene, chloroform, ether, and petroleum ether. Mp 257–258° C. Found, %: C 66.48; H 5.10; N 6.41. Calculated for  $\text{C}_{12}\text{H}_{11}\text{NO}_3$ , %: C 66.35; H 5.10; N 6.49.

**8-Dimethylamino-4-hydroxy-2-methylquinoline 5,6-quinone (VII).** To a solution of 5.0 g (25 mM) of copper acetate in 50 ml of a solution of dimethylamine in ethanol containing 5.4 g (120 mM) of dimethylamine was added 9.65 g (50 mM) of III, and the suspension was stirred in an atmosphere of oxygen. After 3 hr, 1650 ml of oxygen had been absorbed. The reaction mixture was cooled to 0° C, 150 ml of chloroform was added with stirring, and the mixture was acidified with 30 ml of 5 N HCl. Then 200 ml of water was added, the mixture was shaken, the chloroform layer was separated off, and the aqueous layer was extracted with chloroform (2 × 40 ml). The combined chloroform extracts were washed with water (3 × 30 ml), dried with sodium sulfate, evaporated in vacuum to 30 ml, and treated with 75 ml of petroleum ether. The precipitate was filtered off and dried in the desiccator. Yield 7.7 g (86.3%). Brown crystals giving cherry-red solutions. The substance is readily soluble in chloroform, acetone, methanol, ethanol, and acetic acid, moderately soluble in benzene and ethyl acetate, sparingly soluble in water and ether, and insoluble in petroleum ether. Mp 177–178° C (decomp., from ethanol). IR spectrum:  $\nu_{\text{C}=\text{O}}$  1650 and

and 1620  $\text{cm}^{-1}$  (broad band).  $\text{pK}_a$   $6.57 \pm 0.05$  (water, 20° C). Found, %: C 62.00; H 5.21; N 11.97. Calculated for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ , %: C 62.06; H 5.21; N 12.06.

**4-Hydroxy-2-methyl-8-piperidinoquinoline 5,6-quinone (VIII).** A solution of 2.5 g (12.5 mM) of copper acetate in a mixture of 10 ml (100 mM) of piperidine and 30 ml of methanol was treated with 4.83 g (25 mM) of **III**, and the suspension was stirred in an atmosphere of oxygen. After 1.5 hr, 760 ml of  $\text{O}_2$  had been absorbed. The reaction mixture was cooled to 0° C and, with stirring, it was acidified with 125 ml of 1 N HCl. The precipitate was separated off, washed with water, and dried in the desiccator. Yield 4.15 g (61%). Brown crystals readily soluble in chloroform and acetic acid, moderately soluble in benzene and ethyl acetate, sparingly soluble in water and ether, and insoluble in petroleum ether. Mp 176–177° C (decomp., from ethanol). IR spectrum:  $\nu_{\text{C=O}}$  1650 and 1625  $\text{cm}^{-1}$  (broad band),  $\text{pK}_a$   $7.0 \pm 0.1$  (10% ethanol, 20° C). Found, %: C 66.51; H 5.85; N 10.44. Calculated for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$ , %: C 66.10; H 5.92; N 10.28.

**5-Dimethylamino-1-hydroxy-3-methylpyrido[3,2-a]phenazine (IX).** To a solution of 0.46 g (2 mM) of **VII** in 2.5 ml of absolute ethanol heated to the boil was added 0.25 g (2.3 mM) of o-phenylenediamine, and the mixture was boiled for 10 min, left at room temperature for 30 min, and diluted with 10 ml of water after which the precipitate was filtered off and recrystallized from acetone. Yield 0.40 g (66%). Yellow crystals with mp 162–163° C readily soluble in acetic acid, dioxane, and benzene, moderately soluble in acetone, methanol, and ethanol, sparingly soluble in ether and petroleum ether, and insoluble in water. Found, %: N 18.68. Calculated for  $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}$ , %: N 18.41.

**1-Hydroxy-3-methyl-5-piperidinopyrido[3,2-a]phenazine (X).** This was obtained in a similar manner to **IX** from 0.54 g (2 mM) of **VIII** and 0.25 g (2.3 mM) of o-phenylenediamine in 5 ml of ethanol. Yield 0.68 g (98%). Yellow crystals with mp 209–210° C (from toluene) readily soluble in acetic acid, acetone, and chloroform, moderately soluble in dimethylformamide, ether, methanol, and ethanol, sparingly soluble in petroleum ether, and insoluble in water. Found, %: C 73.58; H 5.98; N 16.01. Calculated for  $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}$ , %: C 73.23; H 5.85; N 16.27.

**8-Dimethylamino-4,5,6-trihydroxy-2-methylquinoline (XI).** A) A suspension of 1.16 g (5 mM) of **VII** in 10 ml of ethanol was treated with 0.7 ml (12 mM) of 85% hydrazine hydrate. The temperature of the reaction mixture rose, bubbles of nitrogen were liberated, the solid matter dissolved, and the solution lost its color. Then it was boiled for 5 min, treated with 20 ml of water, and cooled. The precipitate was filtered off, washed with water, and dried in the desiccator. Yield 0.90 g (71.4%). Yellow crystals readily soluble in acetone, acetic acid, methanol, and ethanol, moderately soluble in ether, benzene, and ethyl acetate, sparingly soluble in water, and insoluble in petroleum ether. Mp 223–225° C (from 50% ethanol). Found, %: C 57.13; H 6.22; N 11.16. Calculated for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O}$ , %: C 57.13; H 6.39; N 11.11.

B) To a hot solution of 0.7 g (3 mM) of **VII** in 15 ml of ethanol was added 0.44 g (3 mM) of phenylhydrazine hydrochloride, and the mixture was boiled for 5 min. After 1 hr, the precipitate was filtered off and recrystallized from acetic acid. Yield 0.35 g (43%). Yellow crystals with mp 232–233° C (decomp.), moderately soluble in water and dimethylformamide, sparingly soluble in acetic acid, chloroform, methanol, and ethanol, and insoluble in ethyl acetate, ether, and petroleum ether. Found, %: N 10.20; Cl 13.09. Calculated for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3 \cdot \text{HCl}$ , %: N 10.39; Cl 13.15.

**4,5,6-Trihydroxy-2-methyl-8-piperidinoquinoline (XII).** This was obtained in a similar manner to **XIb** from 0.82 g (3 mM) of **VIII** and 0.44 g (3 mM) of phenylhydrazine hydrochloride. Yield 0.75 g (81%). Yellow crystals with mp 240–242° C, readily soluble in dimethylformamide, acetic acid, and ethanol, moderately soluble in methanol, sparingly soluble in water, dioxane, and ethyl acetate, and insoluble in ether and petroleum ether. Found, %: C 57.65; H 6.16; N 9.06; Cl 11.40. Calculated for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3 \cdot \text{HCl}$ , %: C 57.97; H 6.16; N 9.01; Cl 11.41.

**4,6-Dihydroxy-2-methylquinoline 5,8-quinone (XIII).** A mixture of 50 ml of ethanol and 125 ml of 1 N NaOH was added to 13.9 g

(60 mM) of **VII** (or an equivalent amount of **VIII**) and the mixture was boiled for 15 min. Then it was cooled to 35–40° C and acidified with 50 ml of 4 N HCl; after an hour the precipitate was filtered off, washed with 20 ml of 0.1 N HCl, 20 ml of ethanol, and 40 ml of ether, and dried in the desiccator. Yield 10.4 g (78%). Red substance, moderately soluble in water, sparingly soluble in alcohols, insoluble in nonpolar solvents; on recrystallization from acetic acid it partially decomposes and it does not melt below 350° C. UV spectrum:  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ) in 50% ethanol: 238 (4.30); 350 (3.74); 450 (3.36); 0.1 N NaOH in 50% ethanol: 230 (4.26); 252 (4.28); 385 (3.70). IR spectrum:  $\nu_{\text{C=O}}$  1683 and 1630  $\text{cm}^{-1}$  (broad band).  $\text{pK}_{a1}$   $3.21 \pm 0.02$ ,  $\text{pK}_{a2}$   $9.85 \pm 0.05$  (water, 20° C). Found, %: C 53.78; H 3.94; N 5.98. Calculated for  $\text{C}_{10}\text{H}_7\text{NO}_4 \cdot \text{H}_2\text{O}$ , %: C 53.81; H 4.06; N 6.28.

**1,5-Dihydroxy-3-methylpyrido[3,2-a]phenazine (XIV).** A suspension of 0.45 g (2 mM) of **XIII** in 7 ml of 60% acetic acid was treated at 60° C with 0.25 g (2.3 mM) of o-phenylenediamine and the mixture was boiled for 5 min. After an hour the phenazine produced was filtered off and dried in the desiccator. Yield 0.35 g (63%). Yellow crystals readily soluble in acetic acid, moderately soluble in dioxane, benzene, and chloroform, sparingly soluble in ethyl acetate, acetone, ether, methanol, and ethanol, and insoluble in petroleum ether and water. Mp 253–255° C (from dimethylformamide). UV spectrum  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ) in ethanol: 228 (4.56); 286 (4.56); 418 (4.03); 0.1 N NaOH in 50% ethanol: 238 (4.64); 294 (4.38); 449 (4.11); 0.1 N HCl in 50% ethanol: 238 (4.69); 280 (4.37); 400 (4.08). Found, %: C 69.57; H 4.00; N 15.29. Calculated for  $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_2$ , %: C 69.30; H 4.00; N 15.16.

The IR spectra were taken on a UR-10 spectrophotometer in the form of a suspension in paraffin oil and the UV spectra on a Hitachi (Japan) recording spectrophotometer of type EPS-3.

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