INVESTIGATION OF HETEROCYCLIC QUINONES

XXVI.* OXIDATIVE AMINATION OF 6-HYDROXYQUINOXALINES

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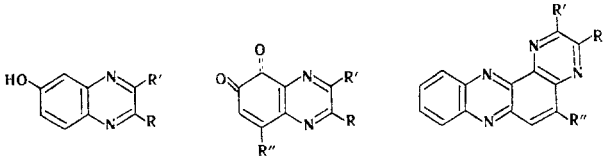
The oxidative amination of 6-hydroxyquinoxalines was studied. O-quinones of the quinoxaline series were obtained for the first time. It is shown that the oxidation of 6-hydroxyquinoxaline is accompanied by amination at C_2 and C_8.

Continuing our study of the oxidation of heterocyclic phenols with oxygen in the presence of a Cu^{2+}–secondary amine complex, we investigated 6-hydroxyquinoxalines, which are interesting for two reasons. First of all, they are of interest because quinoxalines [2, 3] and the intermediates of oxidative amination – 5,6-dihydroxyquinoxalines – are capable of forming copper complexes. Second, it might have been expected that the 2-unsubstituted 6-hydroxyquinoxalines would undergo amination not only at C_8 but, like 6-hydroxybenzothiazoles [4] and 6-hydroxyquinazolines [5], also at C_2.

The oxidation of unsubstituted 6-hydroxyquinoxaline (Ia) proceeds in the presence of secondary amines (pyrrolidine, piperidine, or morpholine) and catalytic amounts of copper acetate. A stoichiometric amount of oxygen (~2 moles) is absorbed during the reaction, and quinoxaline-5,6-quinones containing two secondary amine residues (IIa-c) are formed in good yields. According to the results of thin-layer chromatography (TLC), the reaction proceeds unambiguously without the formation of side products.

In contrast to quinoxaline Ia, the oxidation of 2,3-disubstituted 6-hydroxyquinoxalines (Ib, c) is accompanied by the formation of unidentified side products; this can be explained by assuming the mechanism proposed for amination of heterocyclic quinones [4, 5]: 1,6-addition of secondary amines to quinones IId-f should lead to labile compounds that are incapable of aromatization without cleavage of the C–C bonds. In fact, quinone IIf is quite rapidly converted to a complex mixture of substances under the conditions of oxidative amination.



I a-c II a-f III a-c

I a R=R′=H; b R=R′=CH_3; c R=R′=C_6H_5; II a R=R″=$N(CH_2)_4$, R′=H; b R=R″=$N(CH_2)_5$, R′=H; c R=R″=$N(CH_2CH_2)_2O$, R′=H; d R=R′=CH_3, R″=$N(CH_2)_5$; e R=R′=CH_3, R″=$N(CH_2CH_2)_2O$; f R=R′=C_6H_5, R″=$N(CH_2)_5$; III a R=R″=$N(CH_2)_5$, R′=H; b R=R″=$N(CH_2CH_2)_2O$, R′=H; c R=R′=C_6H_5, R″=$N(CH_2)_5$

Quinones II react with o-phenylenediamine to give yellow phenazine derivatives (IIIa-c).

In addition to the signals of methylene groups of pyrrolidine residues, the PMR spectrum of quinone IIa contains two singlets, one at 5.62 ppm, corresponding to the protons attached to C_7, and the other at 7.83 ppm, which cannot be unambiguously assigned to the proton attached to either C_3 or C_2. In assigning the structure of 2,8-disubstituted quinoxalinequinones to quinones IIa-c, we therefore used only the analogy with other quinones [4, 5] and the IR spectroscopic data as our basis. The IR spectra of the quinones contain two bands of

*See [1] for communication XXV.

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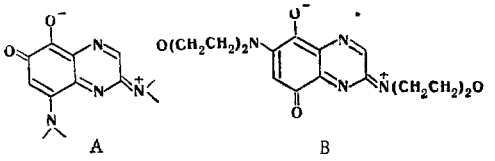
TABLE 1. Quinones II and Pyrazino[2,3-a]phenazines III

Compound	mp, °C (dec.)	IR spectrum, cm⁻¹	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IIa	212—213[a]	1675 1610	$C_{16}H_{18}N_4O_2$	64,3	6,1	18,5	64,4	6,1	18,8	33
IIb	210—211[b]	1679 1622	$C_{18}H_{22}N_4O_2$	66,0	6,7	17,0	66,2	6.8	17,2	49
IIc	223—224[c]	1680 1633	$C_{16}H_{18}N_4O_4$	57,9	5,4	16,7	58.2	5,5	16,7	50
IId	161—162[d]	1699 1606	$C_{15}H_{17}N_3O_2$	66,8	6,0	15,8	66,4	6,3	15,5	19
IIe	187—188[c]	1701 1626	$C_{14}H_{15}N_3O_3$	61,5	5,5	15,6	61,5	5,5	15.4	16
IIf	191—192[e]	1704 1623	$C_{25}H_{21}N_3O_2$	76,2	5,8	10.4	76,0	5.4	10.6	35
IIIa	182—184[e]		$C_{24}H_{26}N_6$			20,9			21,0	73
IIIb	318—319[e]		$C_{22}H_{22}N_6O_2$			20,6			20,9	66
IIIc	301—302[b]		$C_{31}H_{25}N_5$			14,7			15.0	77

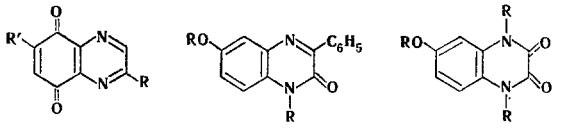
[a] From benzene—heptane.
[b] From dioxane.
[c] From water.
[d] From benzene—petroleum ether.
[e] From ethanol.

carbonyl absorption at 1600-1700 cm^{-1} (Table 1). A comparison of the high-frequency carbonyl maxima shows that the ν_{CO} band in the spectra of quinones IIa-c is shifted by 20-30 cm^{-1} to the long-wave region as compared with IId-f. This shift can be explained by the mesomeric effect of the substituent attached to C_2 (contribution of form A).



A B

For confirmation of the structures of quinones IIa-c, one of them (IIc) was converted to 2,6-dimorpholinoquinoxaline-5,8-quinone (IVb), which was compared with the analogous 2-unsubstituted quinone IVc previously described in [6]. As expected, the carbonyl maximum in the spectrum of quinone IVb is found, due to the contribution of form B, in the higher-frequency region (1667 cm^{-1}) than in the case of quinone IVc (1693 cm^{-1}). This fact serves as an indirect confirmation of amination of quinoxaline Ia at C_2.



IV a-c V a, b VI a, b

IV a R=N(CH2CH2)2O, R'=OCH3; b R=R'=N(CH2CH2)2O; c R=H, R'=N(CH2CH2)2O;
V,VI a R=H; b R=CH3

An attempt was made to extend the oxidative amination to oxo derivatives of quinoxaline. For this, Va and VIa, respectively, were obtained by condensation of 3,4-diaminophenol with ethyl phenylglyoxylate or diethyl oxalate. The formation of isomeric 3-phenyl-7-hydroxy-2-quinoxalone is possible in the synthesis of quinoxalone Va. The structure of Va was proved by its conversion to methoxy derivative Vb, which differs from the isomeric 1-methyl-3-phenyl-7-methoxy-2-quinoxalone [7]. Quinoxalinedione VIa, synthesized by the method described above, cannot be purified, and it was therefore obtained by acid hydrolysis of 2,3-dichloro-6-methoxyquinoxaline; its structure was confirmed by methylation to the previously described VIb [8].

Oxidation of Va and VIa, as well as 6-hydroxyphthalazine-1,4-dione [9], occurs only in the presence of equivalent amounts of copper acetate and leads to a mixture of unidentified products; in our opinion, this is associated with complexing with the participation of —NH—CO— groups.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of deuterochloroform solutions of the compounds were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The following abbreviations were used: s is singlet, m is multiplet, and um is unresolved multiplet. The course of the reactions was monitored by means of TLC on Silufol plates in a chloroform–methanol system (10 : 1).

6-Hydroxyquinoxalines (Ia, b) were obtained by the method in [10], and Ic was obtained by the method in [11].

Oxidation of 6-Hydroxyquinoxaline (Ia). A suspension of 0.73 g (5 mmole) of quinoxaline Ia in a mixture of 20 mmole of secondary amine (10 mmole in the case of pyrrolidine), 6 ml of methanol, and 0.05 g of copper acetate was stirred in an oxygen atmosphere. The reaction was carried out until oxygen absorption ceased (from 1.5 to 4 h). The precipitate was removed by filtration, washed with methanol and ether, and dried. An additional amount of quinone could be isolated from the filtrate. The data on quinones IIa-c are presented in Table 1. PMR spectrum of IIa, δ, ppm: 2.05 um (β-CH_2), 3.61 um (α-CH_2), 5.63 s (7H), and 7.83 s (3H) with an intensity ratio of 8 : 8 : 1 : 1.

Oxidation of 2,3-Disubstituted 6-Hydroxyquinoxalines (Ib, c). A 5-mmole sample of Ib or Ic was oxidized by the method used to oxidize quinoxaline Ia, but 0.5 g (2.5 mmole) of copper acetate was used in the case of Ib, whereas initially 0.1 g and then 0.15 g of copper acetate after 1 h were used in the case of Ic. At the end of oxygen absorption, 50 ml of chloroform was added to the reaction mixture, and the solution was washed successively with water, 200 ml of 1% 3-chelatone solution, water, and dried with Na_2SO_4. The solvent was removed by distillation, and the residue was chromatographed with a column filled with silicic acid with elution of the quinones with chloroform – methanol (100 : 1). Data on quinones IId-f are presented in Table 1. PMR spectrum of IId, δ, ppm: 1.86 um (β,γ-CH_2), 2.68 s (–CH_3), 3.81 um (α-CH_2), and 5.98 is (7H) with an intensity ratio of 6 : 6 : 4 : 1.

Pyrazino[2,3-a]phenazines (IIa-c, Table 1). A 20% excess of o-phenylenediamine was added to a hot solution of quinone IIc (or IIf) in ethanol (in the case of quinone IIb the reaction was carried out in the presence of acetic acid), and the mixture was refluxed for 10 min. The resulting precipitate was removed by filtration (a precipitate of phenazine IIIa formed when the reaction mixture was eluted with water), washed with ethanol, and dried.

2-Morpholino-6-methoxyquinoxaline-5,8-quinone (IVa). A suspension of 1.65 g (5 mmole) of quinone IIc in 10 ml of methanol containing 0.55 g (15 mmole) of HCl was refluxed for 15 min, after which it was cooled, and the resulting precipitate was removed by filtration to give 0.8 g (58%) of red crystals, with mp 259-260° (dec., from ethanol), that were quite soluble in chloroform and acetic acid and only slightly soluble in benzene and dioxane. IR spectrum, cm^{-1}: 1678, 1659, and 1609. Found: C 56.5; H 4.7; N 15.1%. $C_{13}H_{13}N_3O_4$. Calculated C 56.7; H 4.8; N 15.3%.

2,6-Dimorpholinoquinoxaline-5,8-quinone (IVb). A 1.1-g (12.5 mmole) sample of morpholine was added to a suspension of 0.63 g (2.5 mmole) of quinone IVa in 100 ml of ethanol, and the mixture was stirred at room temperature for 16 h. It was then allowed to stand for 2 days. The completion of the reaction was judged from a negative test with cyanoacetic ester [12]. The precipitate was removed by filtration, washed with ethanol and ether, and dried to give 0.64 g (76%) of orange crystals, with mp 238-239° [dec., from dimethylformamide (DMF)], that were quite soluble in chloroform and acetic acid but slightly soluble in dioxane, ethyl acetate, and water. IR spectrum, cm^{-1}: 1667, 1642. Found: C 58.4; H 5.8; N 17.3%. $C_{16}H_{18}N_4O_4$. Calculated: C 58.2; H 5.5; N 17.0%.

3-Phenyl-6-hydroxy-2-quinoxalone (Va). A suspension of 15.4 g (0.1 mole) of 3-nitro-4-aminophenol in 150 ml of methanol was hydrogenated in the presence of a nickel catalyst. At the end of the reduction, 17.8 g (0.1 mole) of ethyl phenylglyoxylate was added to the mixture, and the solution was filtered to remove the catalyst. The filtrate was refluxed for 3 h, after which it was evaporated to 75 ml, and the resulting precipitate was removed by filtration to give 5.2 g (23%) of yellow crystals, with mp 286-287° (from ethanol), that were quite soluble in ethanol but only slightly soluble in water. IR spectrum, cm^{-1}: 3110 (br) and 1660. Found: C 70.7; H 4.3; N 11.8%. $C_{14}H_{10}N_2O_2$. Calculated: C 70.6; H 4.2; N 11.8%.

6-Hydroxyquinoxaline-2,3-dione (VIa). A suspension of 5 g (22 mmole) of 2,3-dichloro-6-methoxyquinoxaline [8] in a mixture of 30 ml of concentrated HBr and 20 ml of acetic anhydride was refluxed for 6 h. The compound initially dissolved, after which a copious amount of precipitate formed. The mixture was diluted

with 200 ml of water, and the precipitate was removed by filtration and dried to give 4 g (92%) of pale-yellow crystals with mp > 360°. The product was soluble in most organic solvents and crystallized from DMF. IR spectrum, cm^{-1}: 3000-3400 (br) and 1600-1700 (br). Found: C 51.1; H 3.4; N 14.8%. $C_8H_6N_2O_3 \cdot {}^1/_2H_2O$. Calculated: C 51.3; H 3.8; N 15.0%.

1-Methyl-3-phenyl-6-methoxy-2-quinoxalone (Vb). A 2-ml sample of dimethyl sulfate was added dropwise with vigorous stirring to a warm solution of 0.4 g (1.7 mmole) of Va in 8 ml of 2 N NaOH solution, after which the mixture was heated on a boiling-water bath for 10 min. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.2 g (45%) of Vb. IR spectrum, cm^{-1}: 1640. Recrystallization of the product from ethanol gave yellow crystals with mp 153-154°. Found: C 72.2; H 5.3; N 10.4%. $C_{16}H_{14}N_2O_2$. Calculated: C 72.2; H 5.3; N 10.5%.

1,4-Dimethyl-6-methoxyquinoxaline-2,3-dione (VIb). Dimethyl sulfate (11.0 ml) was added dropwise with vigorous stirring to a solution of 2 g (11 mmole) of VIa in 70 ml of 2 N NaOH solution, after which the mixture was heated on a boiling-water bath for 10 min. It was then cooled and treated with 30 g of sodium acetate, and the resulting white precipitate was removed by filtration, washed with water, and dried to give colorless crystals, with mp 182-183° (from ethanol) [8], that were moderately soluble in water and ethanol. IR spectrum: 1675 (br) and 1614 cm^{-1}. Found: N 13.1%. $C_{11}H_{12}N_2O_3$. Calculated: N 12.7%.

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