HETEROCYCLIC QUINONES

XII.* 2,4-BIS(DIALKYLAMINO)BENZOTHIAZOLEQUINONES

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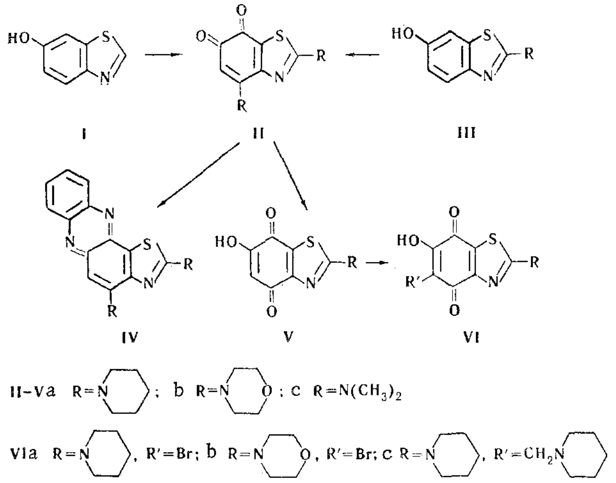
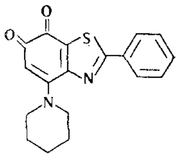
It is shown that 2,4-bis(dialkylamino)benzothiazole-6,7-quinones are formed by the oxidation of 6-hydroxybenzothiazole in the presence of a Cu^{2+}–secondary amine complex. The mechanism of the formation of the compounds obtained is discussed.

We recently described the oxidation of 6-hydroxybenzothiazole (I) by oxygen in the presence of a Cu^{2+}–secondary amine complex resulting in quinones which contain two secondary amine residues [1]. The reaction proceeds with the absorption of 2 moles of oxygen. Structure II was assigned to the compounds obtained. In this communication we present the proof of the structure of these compounds and discuss the mechanism of their formation.

The oxidation of benzoheterocycles with a hydroxy group in the benzene ring (5-hydroxybenzofurans [2], 2-aryl-6-hydroxybenzothiazoles [3], and 6-hydroxyquinolines [4]) leads to dialkylamino-o-quinones. In accordance with the assumed stepwise trend of the reaction [4, 5], 1.5 mole of oxygen is consumed, and the heterocyclic portion of the molecule does not undergo changes. Amination occurs via 1,4-addition of secondary amine to the intermediate o-quinone and subsequent oxidation.

Judging from these results, in the oxidation of I one should expect the formation of quinones which contain one dialkylamino group in the benzene ring.




VII

However, elementary analysis indicated that IIa-c contain two secondary amine residues. The strong absorption at 1600-1700 cm^{-1} (Table 1) indicates the presence of carbonyl groups, while the o-quinoid structure is confirmed by the formation of phenazines IVa-c on reaction with o-phenylenediamine.

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[*] See [13] for communication XI.

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TABLE 1. Characteristics of Quinones II

Compound	mp (dec.)	$\nu_{C=O}$, cm^{-1}	λ_{max}, nm ($lg\ \varepsilon$)	R_f in solvent systems*			Empirical formula	Found, %				Calculated, %				Yield, %
				1	2	3		C	H	N	S	C	H	N	S	
IIa	169,5—170	1626, 1648	231 (2,89) 274 (2,91) 404 (2,79)	0,38	0,82	0,91	$C_{17}H_{21}N_3O_2S$†	61,4	6,2	12,6	9,6	61.6	6,3	12,6	9,6	76
IIb	182—182,5	1628, 1654	238 (2,80) 272 (2,91) 401 (2,95)	0,22	0,28	0,49	$C_{15}H_{17}N_3O_4S$	53,3	5,3	12,6	9,3	53,7	5,1	12,5	9,5	69
IIc	161,5—162,5	1604, 1640	225 (2,95) 270 (2,95) 395 (2,92)	0,26	0,32	0,67	$C_{11}H_{13}N_3O_2S$	52,7	5,3	16,4	12,7	52,5	5,2	16,7	12,7	67

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* System 1: chloroform–methanol (9:1) (on silica gel); system 2: isopropyl alcohol–chloroform (3:7) (on silica gel); system 3: isopropyl alcohol–chloroform (3:7) (on activity II Al_2O_3).

† Molecular weight found 342; calculated 331.

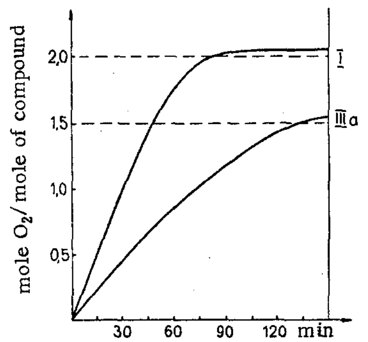

Fig. 1. Dependence of the rate of oxygen absorption on time in the oxidation of I and IIIa (10 mmole of compound, 40 mmole of piperidine, 0.3 mmole of cupric acetate, and 10 ml of methanol).

Determination of the molecular weight of one of the quinones (IIa) indicated that the compound is monomeric. The UV spectra of quinones IIa-c contain three maxima (Table 1), which is characteristic for bicyclic quinones [6, 7]. In addition to the signals of the piperidine protons, the PMR spectrum of IIa contains the sharp singlet of a vinyl proton at 5.50 ppm. The PMR spectrum of quinone VII, obtained under similar conditions, shows the signal of a vinyl proton at 5.70 ppm. These chemical shifts are close to the corresponding values for the vinyl proton of naphthoquinones [8]. The C_2 proton of benzothiazole (δ 8.9-9.6 ppm [9]) is absent in the spectrum of IIa.

Like other dialkylamino-o-quinones [2-4], IIa-c are hydrolyzed by the action of dilute alkali under mild conditions with cleavage of one mole of secondary amine to form hydroxyquinones Va, b. The latter, as vinylogs of carboxylic acids, display acidic properties and dissolve in sodium carbonate and sodium bicarbonate solutions. Bromination and the Mannich reaction for quinones Va and Vb proceed with substitution of the hydrogen at C_5 and lead to the corresponding derivatives VIa-c.

All of the described properties are readily explained if one considers IIa-c to be 2,4-bis(dialkylamino)benzothiazole-6,7-quinones. The definitive confirmation of the structure of the quinones was the synthesis of IIa by means of oxidation of 2-piperidino-6-hydroxybenzothiazole (III) in the presence of piperidine and cupric acetate. The reaction proceeds with the absorption of 1.5 mole of oxygen and leads to a substance which is identical to the product of oxidation of 6-hydroxybenzothiazole under these conditions.

Quinones IIa-c are dark-brown, crystalline substances; their interesting feature is their ability to give solutions of different color, depending on the solvent polarity.

Amination in the 2-position, which occurs on oxidation of 6-hydroxybenzothiazole, can be explained by the decrease in the electron density on the μ-carbon atom of benzothiazole as a result of the electron-accepting effect of the two carbonyl

TABLE 2. Phenazines IV

Compound	mp	Empirical formula	N, %		Yield, %
			found	calculated	
IVa	170—171	$C_{23}H_{25}N_5S$	17,5	17,3	68
IVb	187—189	$C_{21}H_{21}N_5O_2S$	16,9	17,1	51
IVc	167—168	$C_{17}H_{17}N_5S$	21,8	21,6	64

groups in quinone II. The reaction apparently proceeds as 1,2- (or 1,6-) addition, which leads to the formation of the corresponding benzothiazoline. Benzothiazolines are readily oxidized to benzothiazoles [10], which involves the consumption of yet another 0.5 mole of oxygen; this explains the consumption of 2 moles of oxygen in the oxidation of I (Fig. 1).

EXPERIMENTAL

The IR spectra of mineral oil pastes were obtained with an IKS-14a spectrophotometer. The UV spectra of alcohol solutions were obtained with an SF-4A spectrometer. The PMR spectra were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with $CDCl_3$ as the solvent and hexamethyldisiloxane as the internal standard. The molecular weight was determined by isothermal distillation in ethanol with azobenzene as the standard. Thin-layer chromatography was carried out on plates with a fixed layer (Table 1).

6-Hydroxybenzothiazole (I). A solution of 10.0 g of 6-methoxybenzothiazole [11] in 120 ml of 47% HBr was refluxed for 6 h. The crystals that precipitated on cooling were separated, dissolved in 100 ml of water; and a solution of 20 g of sodium acetate in 30 ml of water was added. The resulting precipitate was filtered, washed with water, and recrystallized from alcohol to give 9.05 g (99%) of colorless crystals that were quite soluble in acetone and dioxane, moderately soluble in alcohol; insoluble in petroleum ether and water; and had mp 189.5-190 deg. Found %: C 55.5; H 3.2; N 9.1; S 21.5. C_7H_5NOS. Calc %: C 55.6; H 3.3; N 9.2; S 21.2.

Oxidation of 6-Hydroxybenzothiazole. Compound I (10 mmole) was oxidized in the presence of piperidine, morpholine, or dimethylamine; and the reaction mixture was worked up as described in [1]. A total of 455-470 ml of O_2 was absorbed. Quinones IIIa-c are crystalline, dark-brown substances which are quite soluble in chloroform, methylene chloride, and acetone; moderately soluble in alcohols, dioxane, and benzene; and insoluble in petroleum ether, ether, and water. The results obtained are presented in Table 1.

2-Piperidino-6-methoxybenzothiazole. A mixture of 6.0 g (30 mmole) of 2-chloro-6-methoxybenzothiazole [12] and 15 ml (150 mmole) of piperidine was heated at 120 deg for 4 h; 100 ml of 5% NaOH was added to the reaction mass; and the resulting precipitate was separated, washed with water, dried, and recrystallized from petroleum ether to give 4.8 g (71%) of a product with mp 69-70 deg. Found %: C 62.9; H 6.4; N 11.1; S 13.1. $C_{13}H_{16}N_2OS$. Calc. %: C 62.8; H 6.4; N 11.2; S 12.9.

2-Piperidino-6-hydroxybenzothiazole (IIIa). A solution of 2.5 g of 2-piperidino-6-methoxybenzothiazole in 30 ml of 47% HBr was refluxed for 5 h, neutralized with 10% NaOH; and the resulting precipitate was separated, washed with water, dried, and recrystallized from acetone to give 1.96 g (83%) of a product with mp 223-225 deg. Found %: C 61.6; H 6.3; N 12.3; S 13.5. $C_{12}H_{14}N_2OS$. Calc. %: C 61.5; H 6.0; N 11.9; S 13.6.

Oxidation of IIIa. Compound IIIa [2.36 g (10 mmole)] was oxidized in the presence of 4 ml (40 mmole) of piperidine, and the reaction mixture was worked up according to the method in [1]. After 2.5 h, 340 ml of O_2 was absorbed (Fig. 1). The yield of IIa with mp 169.5-170 deg (dec., from dioxane) was 2.1 g (63.6%). The compound was identical to that obtained by oxidation of 6-hydroxybenzothiazole in the presence of piperidine (IR and UV spectra and R_f value).

Phenazines IV. Anhydrous sodium sulfate (10 g) was added to a solution of 10 mmole of II and 1.2 g (11 mmole) of o-phenylenediamine in 70 ml of dry chloroform, and the mixture was allowed to stand at 18-20 deg for 8-10 days. The sodium sulfate was separated, the chloroform was removed by vacuum distillation, and the residue was recrystallized from aqueous acetone and then from alcohol. The results are presented in Table 2. All of the phenazines were yellow.

2-Piperidino-6-hydroxybenzothiazole-4,7-quinone (Va). Compound IIa [3.31 g (10 mmole)] was added to a solution of 4.0 g (100 mmole) of sodium hydroxide in 100 ml of 50% alcohol, and the mixture was stirred at 18-20 deg for 4 h. The salt of quinone Va was filtered, dissolved in 100 ml of water; and the dark solution was acidified to pH 5.5-6 with 0.1 N HCl. The resulting precipitate was separated; washed with water; and purified by conversion to the sodium salt and liberation by acidification to give 2.11 g (80%) of dark-violet crystals with mp 185-186 deg (dec.) which were quite soluble in alcohol, benzene, dioxane, acetone, and chloroform, and slightly soluble in water. Found %: C 54.3; H 4.5; N 10.3; S 12.8. $C_{12}H_{12}N_2O_3S$. Calc. %: C 54.5; H 4.5; N 10.5; S 12.1.

2-Morpholino-6-hydroxybenzothiazole-4,7-quinone (Vb). This was similarly obtained in 84% yield by saponification of IIb and was obtained as dark-brown crystals which were quite soluble in alcohol, dioxane, acetone, and chloroform; slightly soluble in benzene; and insoluble in water and had mp 241-242 deg (dec.). Found %: C 49.2; H 3.6; N 10.0; S 11.6. $C_{11}H_{10}N_2O_4S$. Calc. %: C 49.6; H 3.7; N 10.5; S 12.0.

2-Piperidino-5-bromo-6-hydroxybenzothiazole-4,7-quinone (VIa). A solution of 0.11 ml (2.1 mmole) of bromine in 5 ml of acetic acid was added to a solution of 0.52 g (2 mmole) of Va and 10 ml of acetic acid, and the mixture was stirred at 18-20 deg for 5 h. It was then diluted with 50 ml of water; and the resulting precipitate was separated, washed with water, dried, and recrystallized from alcohol to give 0.48 g (69.5%) of brown crystals which were slightly soluble in most organic solvents, insoluble in water, and had mp 360 deg. Found %: Br 23.6. $C_{12}H_{11}BrN_2O_3S$. Calc. %: Br 23.2.

2-Morpholino-5-bromo-6-hydroxybenzothiazole-4,7-quinone (VIb). This was similarly obtained by bromination of Vb in 58% yield in the form of brown crystals melting above 360 deg (from alcohol). Found %: Br 23.58. $C_{11}H_9BrN_2O_4S$. Calc. %: Br 23.15%

2-Piperidino-5-piperidinomethyl-6-hydroxybenzothiazole-4,7-quinone (VIc). A solution of 2.46 g (10 mmole) of Va, 1.1 ml (11 mmole) of piperidine, and 1 ml of formalin in 15 ml of alcohol was stirred for 4 h at 18-20 deg; 15 ml of water was added; and the resulting precipitate was separated, washed with water, and dried to give 1.7 g (47%) of a dark-brown substance with mp 232 deg (dec., from alcohol) which was quite soluble in chloroform; slightly soluble in alcohols, dioxane, ethyl acetate, acetone, benzene, and ether; and insoluble in water and petroleum ether. Found %: N 11.8; S 9.21. $C_{18}H_{22}N_3O_3S$. Calc. %: N 11.6; S 8.8.

LITERATURE CITED

1. A. V. Luk'yanov, V. G. Voronin, and Yu. S. Tsizin, Zh. Vsesoyuzn. Khim. Obshchestva, 15, 238 (1970).
2. Yu. S. Tsizin, A. V. Luk'yanov, and M. V. Rubtsov. Khim. Geterotsikl. Soedin., No. 2, 139 (1970).
3. A. V. Luk'yanov, Yu. S. Tsizin, V. G. Voronin, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., No. 3 (1971, in press).
4. Yu. S. Tsizin and M. V. Rubtsov, Khim. Geterotsikl. Soedin., No. 1, 285 (1967).
5. W. Brackman and E. Havinga, Rec. Trav. Chim., 74, 1107 (1955).
6. G. Pettersson, Acta Chim. Scand., 18, 2303 (1964).
7. T. R. Kasturi and T. Aruchalam, Canad. J. Chem., 44, 1088 (1966).
8. P. E. Moore, and P. I. Scheuer, J. Org. Chem., 31, 3272 (1966).
9. L. Lunazzi, F. Taddei, and P. E. Todesco, Boll. Sci. Fac. Chim. Ind. Bologna, 23, 99 (1965).
10. H. P. Lankelma and P. X. Scharnoff, J. Am. Chem. Soc., 53, 2654 (1931).
11. H. H. Fox and M. T. Bogert, J. Am. Chem. Soc., 61, 2014 (1939).
12. H. Erlenmeyer, Helv. Chim. Acta, 25, 515 (1942).
13. N. B. Karpova and Yu. S. Tsizin, Khim. Geterotsikl. Soedin., 1376 (1970).