EXPERIMENTAL

The synthesis of the investigated compounds is described in [2]. The PMR spectra were measured with a JNM-PS-100 spectrometer; the accuracy in the measurement of the chemical shifts was ± 0.05 ppm, and the accuracy in the measurement of the coupling constants was ± 0.5 Hz.

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HETEROCYCLIC QUINONES

XXXIII.* OXIDATIVE AMINATION OF 5(6)-HYDROXYBENZIMIDAZOLES

Yu. S. Tsizin and S. A. Chernyak

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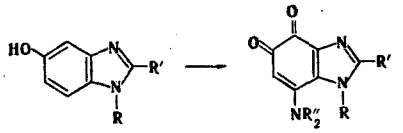
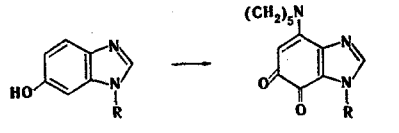
A number of benzimidazole-4,5(6,7)-quinones containing a secondary amine residue in the quinone ring were obtained by oxidation of N-substituted 5(6)-hydroxybenzimidazoles with oxygen in the presence of copper(II)–piperidine (dimethylamine) complexes. It is shown that the reaction proceeds in the presence of catalytic amounts of copper acetate and is not accompanied by amination of the $C_{(2)}$ atom.

The aim of the present research was to study the applicability of oxidative amination for the synthesis of o-benzimidazolequinones, since the existing methods for their preparation are based on the oxidation of difficult-to-obtain bifunctional derivatives [2-5]. For this purpose two fundamental questions had to be answered: Will stable chelate complexes of the products of oxidation of I-III be formed with copper (see [6]), and is amination of the $C_{(2)}$ atom during the oxidation of IV and V possible (as in the case of the previously observed [7] amination of benzothiazole-6,7-quinones)? It should be noted that N-substituted benzimidazole-4,5-quinones have not been previously described.





I R=CH_3, R′=H; II R=C_6H_5, R′=H; III R=C_6H_5, R′=CH_3; IV R=C_6H_5; V R=CH_3; VI R=CH_3, R′=H, NR″$_2$=N$(CH_2)_5$; VII R=C_6H_5, R′=H, NR″$_2$=N$(CH_2)_5$; VIII R=C_6H_5, R′=H, R″=CH_3; IX R=C_6H_5, R′=CH_3, NR″$_2$=N$(CH_2)_5$; X R=C_6H_5, R′=R″=CH_3; XI R=C_6H_5; XII R=CH_3

*See [1] for communication XXXII.

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TABLE 1. Benzimidazolequinones

Compound	mp, °C	$\nu_{C=O}$, cm^{-1}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
VI	168—169[a]	1678, 1627	64,1	6,2	17,1	$C_{13}H_{15}N_3O_2$	63,7	6,2	17,1	22[b]
VII[c]	191—192[d]	1686, 1628	70,0	5,5	13,7	$C_{18}H_{17}N_3O_2$	70,3	5,6	13,7	67
VIII	209—210[a]	1685, 1620	67,6	5,1	16,0	$C_{15}H_{13}N_3O_2$	67,4	4,9	15,7	38
IX	216—217[a]	1676, 1636	71,4	5,9	13,3	$C_{19}H_{19}N_3O_2$	71,0	6,0	13,1	58
X	213—214[e]	1683, 1631	68,0	5,2	14,6	$C_{16}H_{15}N_3O_2$	68,3	5,4	15,0	53
XI[f]	178—179[g]	1680, 1604	69,9	5,2	13,5	$C_{18}H_{17}N_3O_2$	70,3	5,6	13,7	48
XII	175—176[g]	1675, 1597	63,8	6,4	16,9	$C_{13}H_{15}N_3O_2$	63,7	6,2	17,1	55

[a]From ethanol. [b]The quinone was obtained in low yield because of its high solubility in water. [c]UV spectrum, λ_{max} (log ε): 521 (3.37), 347 (4.16), and 238 nm (sh) (4.40). PMR spectrum (at 4-10 ppm): 5.65 (1H, s, CH=C), 7.51-7.65 (5H, m, C_6H_5), and 7.71 ppm (1H, s, CH=N). [d]From dioxane. [e]From water. [f]PMR spectrum (at 4-10 ppm): 5.76 (1H, s, CH=C), 7.30-7.45 (5H, m, C_6H_5), and 7.63 ppm (1H, s, CH=N). [g]From benzene–heptane.

A study of the oxidation of two isomeric series of N-substituted hydroxybenzimidazoles I-III, IV, and V showed that in both cases the reaction proceeds smoothly in the presence of piperidine or dimethylamine and catalytic amounts of copper acetate. In contrast to most of the other heterocyclic phenols, I-V are not oxidized in the presence of morpholine. This can be explained by taking into account the fact that morpholine, which is a weaker base than piperidine, gives less stable complexes with metals [8]. Since hydroxybenzimidazoles are also capable of tying up metal ions [9, 10], the presence in the reaction mixture of both ligands should lead to the following equilibrium:

$$(\text{hydroxybenzimidazole})_n Cu^{2+} \rightleftarrows Cu^{2+} \rightleftarrows (R_2NH)_m Cu^{2+},$$

where R_2NH is a secondary amine. Of course, replacement of the stronger base (piperidine) by a less basic compound (morpholine) leads to a shift in the equilibrium to the left, during which the concentration of the copper–secondary amine complex evidently becomes insufficient for occurrence of the oxidative amination reaction.

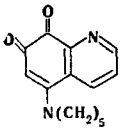
Quinones VI-XII are deeply colored crystalline substances. The quinone structure of these compounds is confirmed by the presence in their IR spectra of two bands of carbonyl absorption (Table 1). In analogy with [11], the low-frequency band can be assigned to the stretching vibrations of the carbonyl group conjugated with the secondary amine residue. One's attention is drawn to the unusually low frequency of the vibrations of the $C_{(6)}=O$ group in the spectra of quinones XI and XII.

The previously synthesized o-benzimidazolequinones are extremely labile [3, 4], whereas, on the other hand, aminoquinones VI-XII are quite stable and can be stored satisfactorily in the solid state. Thus oxidative amination is a simple method for the synthesis of aminobenzimidazole-4,5-quinones and aminobenzimidazole-6,7-quinones that contain alkyl or aryl substituents in the 1 position.

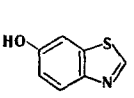
In contrast to quinones XI and XII, isomeric quinones VI-X are capable of forming chelates not only of the O,O type but also the O,N type with the participation of the nitrogen atom of the heteroring [6]. As a rule, the stabilities of the latter are higher; however, both quinones XI and XII and quinones VI-X are formed in the presence of catalytic amounts of copper salts, which indicates the low stabilities of their copper complexes. At the same time, quinolinequinone XIII, which has a similar orientation of the donor atoms, gives an extremely stable copper chelate [6].

On the basis of data on the relative stabilities of complexes of 8-hydroxyquinoline and 4-hydroxybenzimidazoles [12], it may be assumed that the lower stabilities of the copper chelates of benzimidazolequinones VI-X are associated with an increase in the distance between the oxygen and nitrogen atoms and a change in the orientation of the unshared electron pair of the $N_{(3)}$ atom.

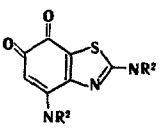
Of the two isomeric quinones VII and XI, only VII gives a slightly soluble complex with $CuCl_2$. The stability of the complex is low – it is decomposed by water and dissociates completely in dilute methanol solutions. The latter fact was established by comparison of the UV spectra of the complex and the free quinone. The data from the IR spectrum of the complex do not make it possible to reliably assign it to the O,O or O,N type (see [6]).



XIII



XIV



XV

It is important that monoaminoquinones XI and XII are formed in the oxidation of IV and V, although the analogous 6-hydroxybenzothiazole XIV gives diaminoquinones XV under these conditions [7]. This difference in the reactivities of benzazole-o-quinones is associated, in our opinion, with the more pronounced donor properties of the $N_{(1)}$ atom as compared with the sulfur atom. As a result of this, the decrease in the electric density on $C_{(2)}$ that is ensured by conjugation with the $C_{(7)}=O$ group and is necessary for amination of the heteroring is "neutralized" to a great extent in the case of benzimidazolequinones, In fact, thiazole is the most electrophilic of the azoles [13].

In conclusion, it should be noted that the oxidation of 5-hydroxybenzimidazole and 5(6)-hydroxybenzimidazolones does not take place with a catalytic amount of copper(II) and that a complex mixture of reaction products from which quinones cannot be isolated is formed in the presence of an equivalent of copper acetate.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of methanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 7-10% solutions of the compounds in deuterochloroform were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. Monitoring of the course of the reactions and the purity of the compounds obtained was accomplished by chromatography on Silufol plates in a chloroform–methanol system (10:1).

1-Methyl-5-hydroxybenzimidazole (I) [14], 1-phenyl-5-hydroxybenzimidazole (II) [15], 1-phenyl-2-methyl 5-hydroxybenzimidazole (III) [14], and 1-methyl-6-hydroxybenzimidazole (V) [16] were obtained by demethylation of the corresponding methoxy derivatives.

1-Phenyl-6-hydroxybenzimidazole (IV). A solution of 2.32 g (10 mmole) of 1-phenyl-6-methoxybenzimidazole [17] in 30 ml of 48% HBr was refluxed for 6 h, after which it was cooled and neutralized with ammonia. The resulting precipitate was removed by filtration, washed with water, and dried to give 1.45 g (69%) of colorless crystals with mp 171-172°C (from benzene). Found: C 74.2; H 5.0; N 13.1%. $C_{13}H_{10}N_2O$. Calculated: C 74.3; H 4.8; N 13.3%.

Benzimidazolequinones VI-XII. A suspension of 5 mmole of hydroxybenzimidazoles I-V in a mixture of 7 ml of methanol, 20 (in the preparation of quinones VI, XI, and XII) or 30 mmole (VII-X) of piperidine or dimethylamine, and 0.1 g (0.5 mmole) of copper acetate was stirred in an oxygen atmosphere until gas absorption ceased (3-4 h). Quinones VII-X precipitated and were removed by filtration, washed with methanol and ether, and dried (an additional amount of quinone could be isolated from the filtrate). For the isolation of quinones VI, XI, and XII the reaction mixture was treated with 150 ml of chloroform, and the solution was washed successively with water, 3% CH_3COOH, and water and dried with magnesium sulfate. The solvent was then removed by distillation, and the residue was crystallized. The yields and constants of the quinones obtained are presented in Table 1.

Copper Complex of Quinone VII. A 1.2-ml sample of a saturated methanol solution of cupric chloride was added to a warm solution of 0.15 g (0.5 mmole) of quinone VII in 15 ml of methanol. After 1 h, the resulting precipitate was removed by filtration, washed with methanol, chloroform, and ether and dried to give 0.14 g (60%) of dark-violet crystals with mp 181-182°C (decomp.). IR spectrum: 1688, 1596, and 1580 cm^{-1}. Found: Cl 16.9; N 8.8%. $C_{18}H_{17}N_3O_2 \cdot CuCl_2$. Calculated: Cl 15.9; N 9.5%.

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STRUCTURE OF TETRAHYDROPYRIDAZINES FORMED FROM 1-ISOPROPYL-3,4-DIMETHYL-1,2-DIAZA-1,3-BUTADIENE AND METHYL VINYL KETONE

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In contrast to the cis isomer, trans-1-isopropyl-3,4-dimethyl-1,2-diaza-1,3-butadiene reacts with methyl vinyl ketone to give a mixture of cis and trans isomers of 5- and 6-acetyl-1-isopropyl-3,4-dimethyl-Δ^2-tetrahydropyridazines. The preponderance of the cis isomer in the case of 5-substituted tetrahydropyridazines constitutes evidence for the existence of secondary orbital interactions of the acetyl group of the dienophile with the C=C bond of the diene component.

The observance of the endo principle [1] for a nucleophilic diene component containing a C=C–N=N fragment [2] has not been investigated. For its verification it was necessary to examine the reaction of olefins with terminally substituted 1,2-diaza-1,3-butadienes.

We have found that α,β-unsaturated azo compounds of this type [3] actually react with methyl acrylate, methyl vinyl ketone, and acrylonitrile to give four-component mixtures of 1,4-cycloaddition products (mixtures of structural isomers and stereoisomers). Their similar physicochemical characteristics made it impossible for us to isolate them in pure form or to reliably identify the Δ^2-tetrahydropyridazines formed, except for the products of the reaction of methyl vinyl ketone with 1-isopropyl-3,4-dimethyl-1,2-diaza-1,3-butadiene (I).

This azadiene exists in the form of Z,E and E,E isomers [3, 4], of which the Z,E isomer, which was isolated in pure form, was found to be inactive in the diene synthesis because of the steric hindrance that arises during its conversion to the s-cis conformation necessary for the reaction. On the other hand, the pure E,E isomer, as expected, readily forms cycloaddition products with methyl vinyl ketone by undergoing the reaction in the cisoid conformation. A mixture of tetrahydropyridazines II–V was isolated from the reaction mixture in 80% yield. The ratio of II–V does not change either during the reaction or during storage, and this constitutes evidence for the absence of interconversions; according to the results of gas–liquid chromatography (GLC), the ratio is 25:17:50:8, respectively. As a result of purification of the mixture by column chromatography, we isolated IV and V in pure form and an inseparable mixture of isomers II and III. (See scheme on next page.)

The results of elementary and spectral analysis of the mixture of II and III and the individual cycloaddition products (IV and V) are in agreement with the Δ^2-tetrahydropyridazine structure. In particular, bands of C=N and C=O bonds are present in their IR spectra (at 1600–1620 and 1730 cm^{-1}), and the UV spectra contain absorption at λ_{max} 240 nm ($\varepsilon \sim 3500$–4000). Singlet signals of a CH_3 group attached to a C=N bond (~1.8–2.0 ppm) and of an acetyl group (~2.0–2.2 ppm), a doublet (J=6.5 Hz) of a methyl group attached to the $C_{(4)}$ atom (~1–1.2 ppm), a septet (J=7 Hz) of the CH portion of a 1-isopropyl grouping (at 3.0–3.5 ppm), and two doublets (J=7.0 Hz) from its diastereotopic methyl groups (~0.8–1.4 ppm) are present in the PMR spectra of

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