246 (7.8); 270 (5.2); 386 (12.6). Found: C 71.4; H 4.6; N 7.2; S 8.3%. $C_{23}H_{18}N_2SO_2$. Calculated: C 71.5; H 4.8; N 7.1; S 8.3%.

All of the remaining III were similarly obtained (Table 1). The reaction times for the preparation of II and IV were 12-25 h (monitoring by TLC). The products were isolated as described above. The physical constants are presented in Table 1.

Mass spectrum of IIIi (m/e): 44 (6.8); (16.6); 55 (11.6). 57 (52.6); 77 (58.2); 78 (18.9); 85 (17.5); 89 (8.8); 91 (6.7); 102 (9.0); 103 (8.3); 116 (16.1); 121 (8.3); 128 (23.8); 129 (9.9); 141 (11.6); 204 (14.9); 205 (16.2); 216 (13.0); 217 (24.5); 218 (100.0); 219 (17.7); 233 (23.9); 234 (5.8); 243 (32.8); 244 (15.8); 245 (15.8); 246 (9.9); 247 (15.5); 248 (14.3); 249 (57.4); 250 (12.5); 270 (9.4) 390 (12.0).

LITERATURE CITED

1. A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 1, 4 (1974).
2. A. K. Sheinkman, G. V. Samoilenko, and N. A. Klyuev, Zh. Obshch. Khim., 44, 1472 (1974).
3. A. K. Sheinkman, S. I. Suminov, and A. N. Kost, Usp. Khim., 42, 1415 (1973).
4. J. Wefer, A. Catala, and F. Popp, J. Org. Chem., 30, 3075 (1965).
5. H. von Dobeneck and W. Goltzsche, Ber., 95, 1484 (1962).
6. A. N. Kost, A. K. Sheinkman, and N. F. Kazarinova, Zh. Obshch. Khim., 34, 2044 (1964).
7. N. Coats and A. Katritzky, J. Org. Chem., 24, 1836 (1959).
8. A. K. Sheinkman, V. A. Ivanov, N. A. Klyuev, and G. A. Mal'tseva, Zh. Org. Khim., 12, 2550 (1973).
9. G. A. Mal'tseva, Master's Dissertation Moscow (1975).
10. N. A. Klyuev, A. K. Sheinkman, R. A. Khmel'nitskii, G. A. Mal'tseva, G. A. Deikalo, and T. V. Stupnikova, Izv. Timiryazev. Sel'skokhoz. Akad., 3, 200 (1974).
11. N. A. Klyuev, R. A. Khmel'nitskii, I. S. Shpileva, and F. L. Kolodin, Zh. Nauchn. Fotograf. Kinematograf., No. 4, 250 (1975).

RESEARCH ON HETEROCYCLIC QUINONES.

XXVIII.* CATALYTIC ACTIVITY OF METAL IONS IN THE AMINATION OF QUINOXALINE-5,8-QUINONES

Yu. S. Tsizin, S. A. Chernyak,
and B. V. Lopatin

UDC 547.863.16:542.958.3

The catalytic activity of metal ions in the amination of quinoxaline-5-8-quinones was studied. It is shown that it changes in conformity with the Irving–Williams order. Proof in favor of the participation of complexes with mixed ligands in the amination is presented. It was observed that two competitive reactions – amination and hydroxylation in the 2 position – are observed in the presence of Cd^{2+} or Zn^{2+}.

In a previous communication [1] we showed that copper ions catalyze the amination of quinoxaline-5,8-quinones at 2-C. This was explained by the formation of a copper chelate complex of the starting quinone. Reactions of quinoline-5,8-quinones that are catalyzed by copper [2] or cerium [3] ions are known. The authors of these papers postulate the formation of chelates, which leads to a decrease in the electron density at 6-C. However, complexing should also increase the sensitivity of the heteroring to nucleophilic attack; in the case of quinoxalinequinones this leads to amination at 2-C. One should have expected that this reaction would not only be catalyzed by copper ions. The aim of the present research was to verify this assumption.

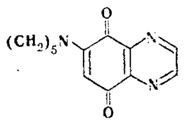
E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow 119830. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 495-499, April, 1977. Original article submitted February 23, 1976; revision submitted July 13, 1976.

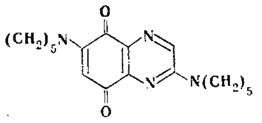
6-Piperidinoquinoxaline-5,8-quinone (I), which reacts rapidly with piperidine in the presence of copper to give 2,6-dipiperidinoquinoxaline-5,8-quinone (II) in high yield [1], was taken as the substrate for this research. The reaction was carried out with the following cations: Li^+, K^+, Mg^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Ag^+, and Hg^{2+}. Precipitates of the hydroxides or complexes are formed when piperidine is added to $CeCl_3$ or $MnSO_4$ solutions, and these cations were therefore not used. The course of the reactions was monitored by thin-layer chromatography (TLC) with a densitometer for quantitative measurements.

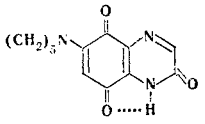
The cations were divided into three groups in conformity with the results obtained. The first group includes metals that are incapable of catalyzing amination – Li^+, K^+, Mg^{2+}, and Ba^{2+}. It is known that the stabilities of their complexes are relatively low [4]. On the other hand, Ag^+ and Hg^{2+} have strong complexing ability and efficiently catalyze the formation of quinone II. However, since an oxidizing agent is necessary for the amination and since these cations have high redox potentials, they are reduced to the metals and removed from the reaction sphere, during which oxygen is not absorbed. In this connection, the reaction goes to completion only in the presence of equivalent amounts of silver (2 moles) or mercury (1 mole) salts.

Finally, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, and Co^{2+} catalyze the amination when less than stoichiometric amounts of them are added. However, all of them have less catalytic activity than copper. It was shown that amination proceeds at comparable rates in the presence of 3 mole % Cu^{2+}, 6 mole % Ni^{2+}, 10 mole % Zn^{2+} or Cd^{2+}, and 30 mole % Pb^{2+} or Co^{2+}. Since the stabilities of metal complexes with various ligands usually change in the order $Zn^{2+} < Cu^{2+} > Ni^{2+} > Co^{2+}$ (the Irving–Williams order [5]), one may note a direct relationship between this parameter and the catalytic acitivities of the metals. It should be noted that when piperidine is replaced by the less basic morpholine, the reaction in the presence of copper is slower, and no reaction occurs with cobalt and cadium.

A compound identified as 6-piperidino-2-quinoxalone-5,8-quinone (III) is formed along with quinone II in the presence of zinc and cadmium. The PMR spectrum of quinone III contains, in addition to signals of piperidine protons (δ 1.71 and 3.72 ppm) and the signal of a proton attached to 7-C (5.93 ppm), a singlet (8.33 ppm) corresponding to the proton attached to 2-C or 3-C. It cannot be unambigouously assigned on the basis of the PMR spectral data, and the IR spectra of quinone III were therefore, studied to establish the position of the amide carbonyl group.


I


II


III

The presence in the IR spectrum in the region of NH frequencies of only one band (3328 cm^{-1}), the position of which does not change on dilution indicates an intramolecular hydrogen bond. In order to ascertain which of the carbonyl groups of quinone III forms this bond, we used the method of isotopic labeling. It is known [6] that when the amino group in amides is deuterated, the C = O band is shifted by ~ 10 cm^{-1} to the low-frequency region. One may also expect a certain but substantially lesser lowering of the frequency of the vibrations of the quinone carbonyl group tied up in a hydrogen bond. At the same time, the frequency of the vibrations of the free carbonyl group should remain practically unchanged.

The IR spectrum of quinone III contains three bands at 1635, 1680, and 1703 cm^{-1} in the region of carbonyl absorption. When it is deuterated,* the maximum of the band at 1703 cm^{-1} is shifted by 9 cm^{-1} to the lower-frequency region, and the band at 1635 cm^{-1} is shifted in the same direction (by 3.5 cm^{-1}); the band at 1680 cm^{-1} retains its original position in the spectrum. This sort of change in the spectrum makes it possible to assign the band at 1635 cm^{-1} to the quinone carbonyl group participating in the formation of a hydrogen bond, the band at 1680 cm^{-1} to the free carbonyl group of the quinone, and the band at 1703 cm^{-1} to the amide group C = O bond. In addition, according to [1, 8], the band at 1680 cm^{-1} can be assigned to the $C_5 = O$ vibration. The oxo group is consequently attached to 2-C.

The high acidity of quinone III (it is soluble in bicarbonate), which is explained by stabilization of the anion through conjugation in the $C_5 = O$ group, also constitutes evidence in favor of this structure. This sort of conjugation is impossible in the isomeric quinone. However, the effect of the $C_8 = O$ group is insignificant, since its acceptor properties are reduced due to conjugation with the piperidine residue.

---

*The deuteration of quinone III by the method described in [7] does not proceed completely.

TABLE 1. Effect of the Reaction Conditions on the Formation of Quinones II and III

Exptl. No.	No. of moles of reagent per mole of quinone I			Conversion of quinone I after 1.5 h, %	Ratio of the quinones, III : I
	amine*	catalyst†	water‡		
1	4	0,1	—	80	1 : 1,6
2	2	0,1	—	57	1 : 1,1
3	2	0,1	4	42	1 : 1,3
4	4	1,0	3	>98	1 : 2,0
5	4	0,1	—	0	—
6	—	0,1	4	0	—
7	4	0,1	—	95	1 : 4,3
8	4	0,1	—	0	—

---

*Piperidine was used as the amine in experiments 1-4, 7, and 8, and pyridine was used in experiment 5. Experiment 6 was carried out without an amine.

†The catalyst in experiments 1-6 was $Cd(CH_3COO)_2 \cdot 3H_2O$; $Zn(CH_3COO)_2 \cdot 2H_2O$ and $p\text{-}CH_3C_6H_4SO_3H \cdot H_2O$ were used in experiments 7 and 8, respectively.

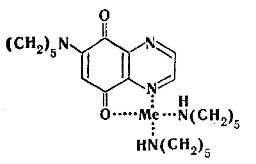
‡The water introduced with the catalyst was disregarded in all cases except experiment 4.

Quinone III may be obtained either as a result of hydroxylation of quinone I or by hydrolysis of quinone II. A special experiment showed that 2,6-dipiperidinoquinoxaline-5,8-quinone (II) is not converted to quinone III under the reaction conditions. The reactions that form these substances are consequently competitive.

As seen from a series of experiments, the results of which are presented in Table 1, the ratio of the quinones depends on the reaction conditions. Since 1 mole of water is formed per mole of quinone during the amination or hydroxylation, it is always present in the reaction mixture in an amount sufficient for the formation of quinone III. At the same time, whereas a decrease in the amount of piperidine, by slowing down the reaction, leads to an increase in the amount of quinone III in the mixture (Table 1, experiment 2), the addition of water, which lowers the reaction rate even more, does not give an increase in the yield of this compound (experient 3). It is important that the reaction does not take place when piperidine is absent (experiments 5 and 6). Both an increase in the amount of cadmium (experiment 4) and replacement of cadmium by zinc (experiment 7) lead to an acceleration of the reaction and a decrease in the amount of quinone III.

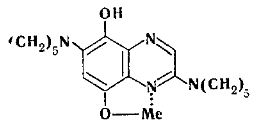
The formation of quinones II and III can be explained by assuming the existence of tetracoordinated complexes with mixed ligands. Complexes with mixed ligands are currently assuming increasing significance (see [9] for a review of this topic), and it is assumed that they are formed in most solutions containing a metal ion and more than one form of ligand [10]. In the amination of a chelate of the IV type the decrease in the activation energy is achieved not only through redistribution of the electron density but also through a decrease in the entropy. Replacement of one of the piperidine molecules within complex IV by a water molecule may lead to the formation of quinone III.

The fact that this reaction does not occur in the presence of acid (experiment 8) constitutes evidence that nucleophilic attack of the heterocyclic portion of quinone I occurs within the complex with mixed ligands.



IV

Me- metal



V

An addition product, which probably has structure V, should be initially formed in the case of amination at 2-C. If the chelating agent is capable of acting as an oxidizing agent (Cu^{2+}, Ag^{+}, and Hg^{2+}), it converts intermediate V to quinone II; otherwise starting quinone I, which has a higher potential, may serve as the oxidizing agent. In this case 1 mole of the hydroquinone corresponding to quinone I is formed per mole of quinone. This scheme is in conformity with the known sequence of reactions of quinones with amines [11].

To confirm the indicated scheme, we carried out the amination in the presence of a metal ion that is not an oxidizing agent — Cd^{2+} — in an anhydrous medium in the absence of oxygen. As a result we obtained a mixture of different amounts of quinones I and II. The hydroquinone corresponding to quinone I cannot be isolated, since it is exceptionally easily oxidized by air oxygen during workup. As expected, quinone III is not formed under these conditions. Thus proof that amination proceeds through a step involving the formation of an intermediate 1,6-addition product has been obtained.

EXPERIMENTAL

The IR spectra 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. Anhydrous methanol and dimethylformamide (DMF) were used in the reactions. Monitoring of the course of the reactions and the quantitative determinations were carried out by TLC on Silufol plates.

Reaction of Quinone I with Piperidine in the Presence of Hg^{2+} or Ag^{+}. A suspension of 0.36 g (1.5 mmole) of quinone I [1] in a mixture of 5 ml of methanol, 0.6 ml (6 mmole) of piperidine, and 1.5 mmole of $Hg(NO_3)_2$ or 3 mmole of $AgNO_3$ was stirred for 1 h, after which the mixture was treated with 30 ml of chloroform, and the precipitated metal was removed by filtration. The filtrate was washed with water and dried with Na_2SO_4, and the solvent was removed by vacuum distillation. The residue was crystallized from aqueous ethanol to give 0.35-0.37 g (70-75%) of bright-red crystals with mp 215-216° (aqueous ethanol). The product was identical to 2,6-dipiperidinoquinoxaline-5,8-quinone (II) [1].

Reaction of Quinone I with Piperidine in the Presence of Ni^{2+}, Co^{2+}, and Pb^{2+}. A suspension of 0.36 g (1.5 mmole) of quinone I in a mixture of 5 ml of methanol, 0.6 ml (6 mmole) of piperidine, and 0.09 mmole of $NiCl_2$ [0.45 mmole of $Pb(OAc)_2$ or $CoCl_2$] was stirred in an oxygen atmosphere until gas absorption ceased (2 h). The precipitate was removed by filtration, washed with methanol and ether, and dried to give 0.30-0.32 g (60-65%) of product. An additional amount of quinone II was isolated from the filtrate. The bright-red crystals had mp 215-216° (aqueous ethanol).

2,6-Dipiperidinoquinoxaline-5,8-quinone (II) and 6-Piperidino-2-quinoxalone-5,8-quinone (III). A suspension of 0.36 g (1.5 mmole) of quinone I in a mixture of 5 ml of methanol, 0.043 g (0.15 mmole) of $Cd(CH_3COO)_2 \cdot 3H_2O$, and 0.6 ml (6 mmole) of piperidine was stirred in an oxygen atmosphere until gas absorption ceased (~2 h), and precipitated quinone II was removed by filtration, washed with methanol and ether, and dried to give 0.18 g (37%) of product with mp 214-215°. The filtrate was dissolved in 30 ml of chloroform, and the solution was washed with 1% HCl and 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 [elution with chloroform—methanol (100:1)]. Two fractions were isolated: the first fraction contained 0.11 g (22%) of quinone II, and the second fraction contained 0.15 g (39%) of quinone III. Quinone III was obtained as dark-violet crystals with mp 181-182° (dec., from dioxane) that were quite soluble in chloroform and bicarbonate and moderately soluble in benzene and water. IR spectrum ($CHCl_3$): 3328 (NH), 1703 (C = O, amide I), 1680 (C_5 = O), and 1636 cm^{-1} (C_8 = O); KBr pellet: 3300 w (broad NH), 3065 m (C_{ar}—H), 2929 m (CH_2), 1680 s (C_5 = O), 1669 vs (C = O, amide I), 1629 vs (C_8 = O), 1602 m, 1553 s, and 1540 cm^{-1} w. PMR spectrum (at 1-10 ppm), δ: 1.71 (β, γ-CH_2, unresolved multiplet), 3.72 (α-CH_2, unresolved multiplet), 5.93 (7H, singlet), and 8.33 ppm, (3H, singlet); intensity ratio 6:4:1:1. Found: C 60.4; H 5.4; N 16.0%. $C_{13}H_{13}N_3O_3$. Calculated: C 60.2; H 5.1; N 16.2%.

Study of the Conditions for the Formation of Quinone III. A suspension of 0.12 g (0.5 mmole) of quinone I in 3 ml of methanol containing the other reagents in the amounts indicated in Table 1 was stirred in an oxygen atomosphere for 1.5 h, after which the mixture was dissolved in 20 ml of chloroform, and the solution was washed with 20 ml of 1% HCl and two 10-ml portions of water and dried with Na_2SO_4. The relative percentages of the quinones in the resulting mixture were determined by TLC. Chromatography was carried out on Silufol plates in an acetone—ethyl acetate—chloroform system (1:1:1). Three spots corresponding to quinones I (R_f 0.48), II (R_f 0.75), and III (R_f 0.32) were observed. The method in [12], based on the relationship between the density of the color of the spot on the chromatogram and the intensity of the light reflected from them, which is described by the Lambert—Beer—Bouguer formula, was used for quantitative analysis of the chromatograms. A condition for the applicability of this method is a linear relationship between the color of the spots and the amount of substance over the investigated range of concentrations.

The measurements were made with an ERI-65m densitometer (VEB Karl Zeiss, Jena, German Democratic Republic), which records both the optical density and its integral. Steps of different height correspond to each spot on the integral curve. The height of the step (integral intensity) after introduction of a correction for the differences in the coefficients of reflection gives direct representations of the quantitative ratios of the substances on the chromatograms, since the form of the spot does not affect the integral intensity.

The relative percentages of the quinones (in mole percent) were calculated from the formula

$$c_i = \frac{k_i a_i}{\sum\limits_i k_i a_i} \cdot 100,$$

where a_i is the integral intensity of the i-th spot on the densitogram, and k_i is a corrective factor that takes into account the differences in the coefficients of reflection. The summation was performed over the intensities of all of the spots on the chromatograms. The k_i values (1.00, 1.07, and 1.75, respectively, for quinones III, I, and II) were determined from the densitometric measurements of the chromatograms of a standard mixture of different weight amounts of the quinones, in which the molar concentrations were in a ratio of 0.97:1.0:0.78 (III:I:II).

The measurements of the chromatograms, to which solutions of the samples with concentrations both higher and lower than those usually employed ($2.5 \cdot 10^{-2}$ mole/liter), showed a linear relationship between the integral intensity and the concentrations over a broad range. Five chromatograms were obtained and measured for each sample. The error in the measurements did not exceed 2.5%. The results are presented in Table 1.

Reaction of Quinone I with Piperidine in the Presence of Cd^{2+} in an Oxygen-Free Medium. A 0.43-g (1.5 mmole) sample of $Cd(CH_3COO)_2 \cdot 3H_2O$ was dissolved in 3 ml of DMF, 0.3 g of Na_2SO_4 and 0.36 g (1.5 mmole) of quinone I were added, and the mixture was stirred in a stream of dry nitrogen for 30 min. Piperidine [0.6 ml (6 mmole)] was added, and the mixture was stirred in a nitrogen atmosphere for another 4 h. It was then dissolved in 50 ml of chloroform, and the solution was washed with 1% hydrochloric acid and water and dried with Na_2SO_4. According to the TLC data, the mixture contained quinones I and II in a ratio of 1:1.

LITERATURE CITED

1. S. A. Chernyak and Yu. S. Tsizin, Khim. Geterotsikl. Soedin., No. 12, 1672 (1976).
2. E. J. Corey and H. Konig, J. Chem. Soc., 84, 4904 (1962).
3. Y. T. Pratt, J. Org. Chem., 27, 2905 (1962).
4. A. A. Grinberg, Introduction to the Chemistry of Complexes [in Russian], Khimiya, Leningrad (1971), p. 556.
5. H. Irving and R. J. P. Williams, J. Chem. Soc., 3202 (1953).
6. V. West (editor), Applications of Spectroscopy in Chemistry [Russian translation], Inostr. Lit., Moscow (1959), p. 416.
7. I. Suzuki, Bull. Chem. Soc. Jpn., 35, 1279 (1962).
8. Yu. S. Tsizin and S. A. Chernyak, Khim. Geterotsikl. Soedin., 982 (1976).
9. H. Sigel, Angew. Chem., Int. Ed., 14, 394 (1975).
10. D. D. Perrin, I. G. Sayce, and V. S. Sharma, J. Chem. Soc., A, 1 755 (1967).
11. L. Fieser and M. Fieser, Organic Chemistry [Russian translation], Vol. 2, Khimiya, Moscow (1966), p. 411.
12. E. Heinish and H. Hornavsky, Jena Review, 130 (1970).