INVESTIGATION OF HETEROCYCLIC QUINONES

XXVII.* CATALYSIS OF THE REACTION OF QUINOXALINE-5,8-QUINONES WITH AMINES BY COPPER IONS

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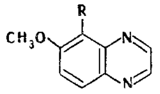
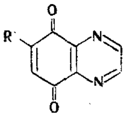
It is shown that copper ions catalyze the amination of 6-morpholino(piperidino)quinoline-5,8-quinone with secondary amines at the C_2 atom. The role of bidentate copper complexes in this process is discussed.

We have previously shown that quinoline-5,6-quinones containing a secondary amine residue not only in the quinoid ring (attached to C_8) but also in the heterocyclic ring (attached to C_2 [1]) are formed in the oxidation of 6-hydroxyquinoline with oxygen in the presence of a Cu^{2+}–secondary amine complex. Moreover, it is known that quinoxaline-5,8-quinones react with primary and secondary amines in glyme to give only 6-aminoquinoxaline-5,8-quinones [2]. In the present research we ascertained the conditions under which p-quinoxalinequinones are capable of undergoing amination in the heterocyclic fragment of the molecule.

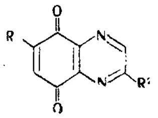
Quinones V and VI, obtained by replacement of the methoxy group of quinone IV by a secondary amine, were used as the starting compounds. Compound IV was synthesized from 6-methoxyquinoxaline (I) by nitration, reduction of the nitro group, and oxidation of the resulting aminoquinoxaline III with potassium iminoxyldisulfonate [3].



I–III



IV–VI



VII–IX

I R = H II R = NO_2, III R = NH_2, IV $R^1 = OCH_3$, V, IX $R^1 = N(CH_2CH_2)_2O$
VI $R^1 = N(CH_2)_5$ VII $R^1 = R^2 = N(CH_2CH_2)_2O$ VIII $R^1 = R^2 = N(CH_2)_5$ IX $R^2 = N(CH_2)_5$

Traces of diaminoquinones are not detected when quinones V and VI are heated with secondary amines in methanol, benzene, or dimethylformamide [DMF]. However, in the presence of catalytic amounts of copper salts, quinones react with secondary amines at room temperature to give diaminoquinones VII–IX in high yields. The structure of VII–IX as 2,6-disubstituted quinoxaline-5,8-quinones was determined unambiguously, since one of the substances (VII) is identical to that previously obtained in [1].

In polar solvents such as methanol, ethanol, or DMF, amination proceeds rapidly and goes to completion in the presence of oxidizing agents. Air oxygen is usually sufficient, but divalent copper acts as the oxidizing agent in an oxygen-free medium. In this case a stoichiometric amount of copper salt corresponding to the $Cu^{2+} \rightarrow Cu^{+}$ transition is necessary for completion of the reaction. The reverse transformation [4] is readily realized under the influence of oxygen, and a catalytic amount of copper is sufficient.

It should be noted that copper ions catalyze only the reaction with secondary amines – primary amines and ammonia do not react under these conditions. Similar facts [5, 6] have been noted in the case of a number of benzo- and naphthoquinones.

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*See [1] for communication XXVI.

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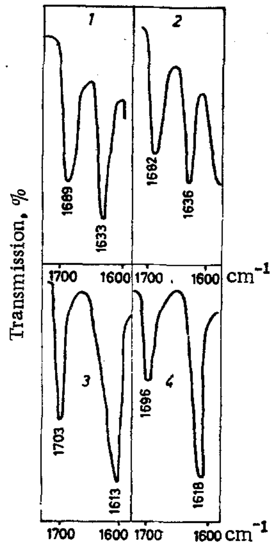
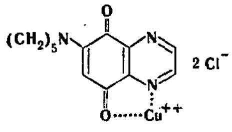
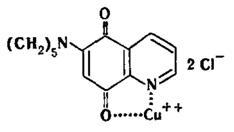


Fig. 1. IR spectra of quinoxaline- and quinoline-5,8-quinones and their complexes with $CuCl_2$: 1) 6-piperidinoquinoxaline-5,8-quinones (VI); 2) 6-piperidinoquinoline-5,8-quinone; 3) complex of 6-piperidinoquinoxaline-5,8-quinone with $CuCl_2$ (X); 4) complex of 6-piperidinoquinoline-5,8-quinone with $CuCl_2$ (XI).

Having assumed that the catalytic effect of copper is associated with complexing, we obtained the complex of quinone VI with cuprous chloride, which, according to the results of elementary analysis has a metal to ligand ratio of 1 : 1. Taking into account the high stabilities of chelate complexes and the increased electron density on the $C_8=O$ carbonyl oxygen (due to conjugation with the piperidine residue), one should have expected the formation of a complex with structure X.

To establish its structure we synthesized the model compound 6-piperidinoquinoline-5,8-quinone, which reacted with $CuCl_2$ to give a complex also having an 1 : 1 composition. A study of the IR spectra of the ligands and the complexes made it possible to assign structures X and XI to the latter.


X


XI

The IR spectrum of quinone VI contains two bands of carbonyl absorption at 1689 ($C_5=O$) and 1635 cm^{-1} ($C_8=O$); the latter is shifted to the long-wave region under the influence of the piperidine residue [1]. As expected [7], complexing gives rise to a further decrease in the $C_8=O$ frequency (by 22 cm^{-1}); however, the $C_5=O$ frequency, on the other hand, is increased by 14 cm^{-1} owing to the development of an acceptor chelate ring. Similar changes in the carbonyl frequencies are also observed in the case of the model compound, in which the formation of a chelate ring is possible only with the participation of the $C_8=O$ carbonyl group.

The copper ion in the complex with quinones V or VI gives rise to a decrease in the electron density on C_2 and thereby facilitates nucleophilic attack at this position.

The reaction of complex X with piperidine proceeds very vigorously, since replacement of quinone VI by its copper complex is equivalent to the use of an equimolar amount of coopper salt, which leads to a sharp increase in the reaction rate.

The copper chelates of quinones VII-IX cannot be isolated; this constitutes evidence for their lower stabilities as compared with the complexes of quinones V or VI. This difference shows up graphically when chloroform solutions of the quinones are shaken with an aqueous $CuCl_2$ solution. The aqueous layer is decolorized with quinones V and VI, whereas it retains its blue color with quinones VII-IX. In conclusion, it should be noted that the described scheme for the participation of copper in the amination reaction is approximate, since the presence in the reaction mixture of excess secondary amine, which can give copper complexes and, together with quinones, complexes with mixed ligands, was disregarded.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of deuterochloroform solutions were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard; the following abbreviations were used: s is singlet, and um is unresolved multiplet. The course of the reactions and the purity of the products were monitored by means of thin-layer chromatography (TLC) on Silufol plates in an ethyl acetate–acetone system (3 : 1).

6-Methoxyquinoxaline (I). A 30-ml sample of an 80% hydrazine hydrate solution was added in the course of an hour with stirring at 40° to a solution of 33.6 g (0.2 mole) of 3-nitro-4-aminoanisole in 200 ml of methanol, after which the mixture was stirred at 40° for another 30 min and on a water bath for 1 h. The catalyst was then removed by filtration, the filtrate was vacuum evaporated to 70 ml, and 140 ml of water, 53.2 g (0.2 mole) of the bisulfite derivative of glyoxal, and 30 g (0.36 mole) of sodium acetate were added to the solution. The mixture was heated on a water bath for 3 h, after which it was cooled and treated with 100 ml of a 2 N sodium hydroxide solution. The resulting precipitate was removed by filtration, washed with water, and dried to give 22.5 g (70%) of a product with mp 54°. Vacuum distillation at 158-160° (20 mm) gave 19.5 g (60.5%) of colorless crystals with mp 59-60° [bp 128° (7 mm) and mp 60° [8]]. IR spectrum, cm^{-1}: 1618 and 1500 (arom.).

5-Nitro-6-methoxyquinoxaline (II). A 7.6-g (0.075 mole) sample of powdered potassium nitrate was added with stirring at room temperature in the course of 45 min to a solution of 10 g (0.06 mole) of 6-methoxyquinoxaline in 100 ml of concentrated sulfuric acid. At the end of the addition, the mixture was stirred for another hour, after which it was poured over 1 kg of ice. The resulting precipitate was removed by filtration, washed with water, and dried to give 9.8 g (79%) of pale-yellow crystals with mp 207-208° (from benzene). IR spectrum, cm^{-1}: 1536 and 1310 (NO_2). Found: N 20.3%. $C_9H_7N_3O_3$. Calculated: N 20.5%.

5-Amino-6-methoxyquinoxaline (III) Hydrochloride. A suspension of 3.7 g (0.185 mole) of II in 35 ml of methanol was hydrogenated in the presence of 0.1 g of Raney nickel at room temperature and standard pressure. After hydrogen absorption ceased, the mixture was heated to 50° and filtered. The filtrate was cooled and treated with a methanol solution of HCl up to pH 2, and the mixture was vacuum evaporated to dryness. The residue was triturated with 5 ml of methanl, and the solid material was removed by filtration, washed with methanol and ether, and dried to give 2.6 g (71%) of colorless crystals with mp > 360° (from methanol). IR spectrum, cm^{-1}: 3270 (NH); 1644, 1576, 1530, and 1505 (arom.). Found: Cl 17.1%. $C_9H_9N_3O \cdot HCl$. Calculated: Cl 16.8%. 5-Amino-6-methoxyquinoxaline benzoate had mp 155-156° (from benzene). IR spectrum, cm^{-1}: 3203 (NH); 1639 (C = O) and 1610 (arom.). Found: N 15.1%. $C_{16}H_{13}N_3O_2$. Calculated: N 15.2%.

6-Methoxyquinoxaline-5,8-quinone (IV). A solution of 0.42 g (2 mmole) of the hydrochloride of III in 30 ml of water was added with stirring at room temperature in the course of 1 h to a solution of 1.33 g (4.4 mmole) of potassium iminoxyldisulfonate [9] and 1.2 g (10 mmole) of NaH_2PO_4 in 100 ml of water, and the mixture was allowed to stand overnight. It was then saturated with NaCl, and the quinone was extracted with chloroform (six 30-ml portions). The combined extracts were washed with a saturated NaCl solution and dried with sodium sulfate. The solvent was removed by distillation, the residue was triturated with acetone, and the solid material was removed by filtration to give 0.25 g (65%) of pale-yellow crystals with mp 235-236° (dec., from water); the product was moderately soluble in water and chloroform. IR spectrum, cm^{-1}: 1698, 1657 (C = O); 1603, 1567, and 1530 (arom.). Found: C 56.8; H 3.5; N 14.4%. $C_9H_6N_2O_3$. Calculated: C 56.9; H 3.2; N 14.7%. In contrast to most of the other quinones, IV gave a positive Craven test [10] (green rather than blue).

6-Morpholinoquinoxaline-5,8-quinone (V). A suspension of 0.38 g (2 mmole) of quinone IV in a mixture of 5 ml of ethanol and 0.54 ml (6 mmole) of morpholine was refluxed for 1 h, after which it was cooled, and the solid material was removed by filtration, washed with methanol and ether, and dried to give 0.42 g (86%) of bright-red crystals with mp 220-221° (dec., from glyme). IR spectrum, cm^{-1}: 1693, 1640 (C = O); 1578, 1550 (arom.) (see [2]).

6-Piperidinoquinoxaline-5,8-quinone (VI). This compound was obtained from 2 mmole of quinone IV and 6 mmole of piperidine by the method used to prepare quinone V, except that the reaction mixture was stirred at 40-50°. Workup gave bright-red crystals, with mp 170-171° (dec., from benzene), in 78% yield; the product was quite soluble in chloroform, moderately soluble in benzene, and only slightly soluble in water and ether. IR spectrum, cm^{-1}: 1689, 1633 (C = O); 1582, 1560 (arom.). PMR spectrum, δ, ppm: 1.76 um (β,γ-CH_2); 3.65 um (α-CH_2); 6.18 s (7H); 8.85 um (2H, 3H), with an intensity ratio of 6 : 4 : 1 : 2. Found: C 64.4; H 5.5; N 17.5%. $C_{13}H_{13}N_3O_2$. Calculated: C 64.2; H 5.4; N 17.3%.

Copper Complex of Quinone VI (X). A total of 2 ml of a saturated methanol solution of cupric chloride (0.15 g/ml) was added to a warm solution of 0.24 g (1 mmole) of 6-piperidinoquinoxaline-5,8-quinone in 3 ml of methanol, and the resulting precipitate was removed by filtration, washed with warm methanol and ether, and dried to give 0.36 g (95%) of bright-red crystals with mp 177-178°; the product was only slightly soluble in water and most organic solvents. IR spectrum, cm^{-1}: 1703, 1613 (C=O); 1561, 1533 (arom.). Found: C 41.1; H 4.3; N 10.1; Cl 17.5%. $C_{15}H_{13}N_3O_2 \cdot CuCl_2$. Calculated: C 41.5; H 3.5; N 11.1; Cl 18.8%.

Copper Complex of 6-Piperidinoquinoline-5,8-quinone (XI). This compound was obtained as in the preceding experiment from 6-piperidinoquinoline-5,8-quinone [11]. Workup gave red crystals with mp 175-176° in 83% yield; the product was only slightly soluble in most organic solvents and water. IR spectrum, cm^{-1}: 1696, 1618 (C=O); 1533 (arom.). Found: C 44.9; H 4.0; N 18.0; Cl 17.9%. $C_{14}H_{14}N_2O_2 \cdot CuCl_2$. Calculated: C 44.8; H 3.5; N 17.5; Cl 18.9%.

2,6-Dimorpholinoquinoxaline-5,8-quinone (VII). A suspension of 0.36 g (1.5 mmole) of quinone V in a mixture of 3 ml of methanol, 0.54 ml (6 mmole) of morpholine, and 0.05 mmole of cupric acetate or chloride, was stirred in an oxygen atmosphere until gas absorption ceased (less than 1 h). The precipitate was removed by filtration, washed with methanol and ether, and dried to give 0.41 g (82%) of bright-red crystals with mp 238-239° (dec., from DMF). The product was identical to the compound obtained in [1].

2,6-Dipiperidinoquinoxaline-5,8-quinone (VIII). This compound was obtained by reaction of quinone VI with piperidine, as in the preparation of quinone VII. Workup gave bright-red crystals with mp 215-216° (dec., from aqueous ethanol) in 65% yield; the product was quite soluble in chloroform, moderately soluble in alcohol, and only slightly soluble in water and ether. IR spectrum, cm^{-1}: 1664, 1618 (C=O); 1570, 1517 (arom.). Found: C 66.0; H 6.5; N 17.0%. $C_{18}H_{22}N_4O_2$. Calculated: C 66.2; H 6.8; N 17.2%.

2-Piperidino-6-morpholinoquinoxaline-5,8-quinone (IX). This compound was obtained by reaction of quinone V with piperidine, as in the preparation of quinone VII. Workup gave bright-red crystals with mp 229-230° (dec., from dioxane) in 70% yield. IR spectrum, cm^{-1}: 1664, 1641 (C=O); 1559, 1515 (arom.). Found: C 62.1; H 6.2; N 17.3%. $C_{17}H_{20}N_4O_3$. Calculated: C 62.2; H 6.1; N 17.1%.

Reaction of Complex X with Piperidine. A 0.3-ml (3 mmole) sample of piperidine was added to a suspension of 0.57 g (1.5 mmole) of complex X in 3 ml of methanol, and the mixture was cooled and stirred in an oxygen atmosphere until gas absorption ceased (~10 min). It was then dissolved in chloroform, and the chloroform solution was washed with 3% acetic acid and water and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was crystallized twice from aqueous ethanol to give 0.2 g (42%) of bright-red crystals with mp 215-216°. The product was identical to quinone VIII.

Amination of Quinone VI in the Absence of Oxygen. A solution of 0.37 g (1.5 mmole) of quinone VI in a mixture of 3 ml of DMF, 0.6 ml (6 mmole) of piperidine, and 0.6 g (3 mmole) of cupric acetate was stirred in a stream of nitrogen for 1 h, after which it was dissolved in 60 ml of chloroform and the solution was washed successively with water, 1% HCl, and water. The chloroform solution was dried with Na_2SO_4, the solvent was removed by vacuum distillation, and the residue was crystallized from aqueous ethanol to give 0.3 g (60%) of bright-red crystals with mp 215-216°. The product was identical to quinone VIII.

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