RESEARCH ON BENZIMIDAZOLE DERIVATIVES

XL.* REACTION OF MERCAPTO DERIVATIVES OF AZOLES WITH HALOQUINONES

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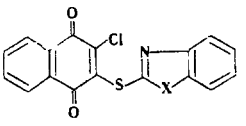
Mercapto derivatives of benzimidazole and imidazole undergo condensation with 2.3-dichloro-1,4-naphthoquinone to give 1.4-naphthoquinonyl derivatives, which can be cyclized to dioxo derivatives of condensed azole systems.

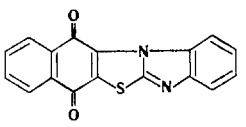
Up to now, the reaction of mercapto derivatives of nitrogen heterocycles with haloquinones has not been studied. We therefore subjected mercapto-substituted benzimidazoles and imidazoles to reaction with 2.3-dichloro-1,4-naphthoquinone (I), chloranil (II), and 2,3-dichloro-5.6-dicyano-1,4-benzoquinone (III).

The azole mercapto derivatives react with I at the mercapto group. 2-Mercaptobenzothiazole and 2-mercaptobenzoxazole form sulfides IV and V, the structures of which are confirmed by the IR spectral data. The reaction of I with 2-mercaptobenzimidazole, 2-mercapto-4.5-diphenylimidazole, and 4,5-phenylmercaptoimidazole does not stop at the step involving the formation of the sulfides but leads to polycyclic quinones VI-VIII, respectively, which are red relatively high-melting substances that are insoluble in dilute acids and alkalis.

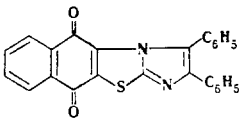


IV X=S; V X=O

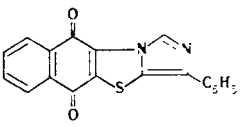
When they are heated with zinc in acetic anhydride they are reduced to hydroquinones.



VI



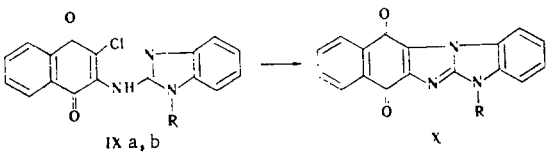
VII



VIII

We were unable to realize similar transformation with quinones II and III; a mixture of darkly colored substances that are not amenable to purification is formed as a result of the reaction. The reaction of 2-mercaptobenzothiazole with II leads to di(2-benzothiazolyl) disulfide.

We also carried out experiments on the synthesis of polycyclic quinones starting from 2-amino derivatives of benzimidazole. As in [2], quinones IXa, b were obtained.



IX a, b X

IX a R=C_2H_5; b R=$CH_2C_6H_5$

*See [2] for communication XXXIX.

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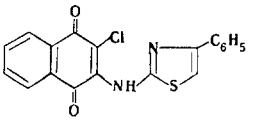
Quinone X was obtained when IXa was refluxed in glacial acetic acid. Reaction of 2-amino-4-phenylthiazole with I gave XI, which cannot be cyclized even when it is refluxed for many hours in glacial acetic acid, o-xylene, and diethylene glycol.



XI

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

2-(2-Benzothiazolylthio)-3-chloro-1.4-naphthoquinone (IV). A mixture of 1.67 g (10 mmole) of 2-mercaptobenzothiazole. 2.27 g (10 mmole) of I, and 0.90 g (11 mmole) of anhydrous sodium acetate in 20 ml of alcohol was stirred and refluxed for 1 h, and the resulting precipitate was removed by filtration and washed successively with alcohol, water, and several times with alcohol to give 2.70 g (75%) of red prisms with mp 177-178° (from dioxane–alcohol). IR spectrum: 1680 and 1665 cm^{-1} (CO); the absorption band of the C=S bond was absent. Found: C 57.4; H 2.7; Cl 9.8; S 17.6%. $C_{17}H_8ClNO_2S_2$. Calculated: C 57.1; H 2.3; Cl 9.9; S 17.9%.

2-(2-Benzoxazolylthio)-3-chloro-1.4-naphthoquinone (V). This compound was obtained by the method used to prepare IV. Workup gave 2.06 g (60%) of shiny red-orange plates with mp 194-195° (from dioxane containing alcohol). IR spectrum: 1680 and 1668 (CO); the absorption band of the C=S bond was absent. Found: C 60.2; H 2.7; Cl 10.1; S 9.8%. $C_{17}H_8ClNO_3S$. Calculated: C 59.9; H 2.4; Cl 10.4; S 9.4%.

Benzimidazo[2,1-b]naphtho[2,3-d]thiazole-7.12-dione (VI). A 1.8-g (12 mmole) sample of 2-mercaptobenzimidazole and 1.8 g (22 mmole) of anhydrous sodium acetate were added to a hot solution of 2.27 g (10 mmole) of I in 200 ml of alcohol, and the mixture was stirred and refluxed for 1.5 h. The resulting precipitate was removed by filtration, washed with 5 ml of alcohol, and dried to give 2.15 g (70.7%) of dark-orange needles with mp 250-251° (from dioxane containing alcohol; the compound softened 2° below its melting point). The product was insoluble in alkalis and dilute acids but quite soluble in concentrated sulfuric acid and hot concentrated hydrochloric acid. IR spectrum: 1665 cm^{-1} (CO). Found: C 67.5; H 2.9; N 8.9; S 10.6%. $C_{17}H_8N_2O_2S$. Calculated: C 67.1; H 2.7; N 9.2; S 10.5%.

2.3-Diphenylimidazo[2,1-b]haphtho[2,3-d]thiazole-5,10-dione (VII). A solution of 2.27 g (10 mmole) of I, 2.25 g (10 mmole) of 2-mercapto-4.5-diphenylimidazole, and 1.8 g (22 mmole) of anhydrous sodium acetate was refluxed in 100 ml of alcohol for 2.5 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration and washed with alcohol and water to give 2.73 g (67%) of dark-red needles with mp 286-287° (from dioxane containing alcohol). IR spectrum: 1660 and 1650 cm^{-1} (CO). Found: C 73.4; H 3.3; N 8.5; S 7.5%. $C_{25}H_{14}N_2O_2S$. Calculated: C 73.8; H 3.5; N 8.7; S 7.9%.

3-Phenylimidazo[5,1-b]naphtho[2,3-d]thiazole-5,10-dione (VIII). A 4.54-g (20 mmole) sample of I was added to a hot solution of 3.52 g (20 mmole) of 4.5-phenylmercaptoimidazole in 120 ml of alcohol and 4 ml of concentrated hydrochloric acid, and the mixture was stirred and refluxed for 30 min. A 6.56-g (80 mmole) sample of anhydrous sodium acetate was added, and the mixture was refluxed for another 2 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with 100 ml of water to give 4.2 g (64%) of fine dark-red plates with mp 248-249° (from isopropyl alcohol containing chloroform). IR spectrum: 1660 cm^{-1} (CO). Found: C 68.9; H 3.0; N 8.9; S 9.2%. $C_{19}H_{10}N_2O_2S$. Calculated: C 69.1; H 3.1; N 8.5; S 9.7%.

Quinones IXa, b and XI were obtained by the following method. A solution of 0.05 mole of the corresponding 2-amino derivatives of benzimidazole or thiazole and 0.05 mole of I in 150 ml of alcohol was refluxed for 20 h, during which 2 g of anhydrous sodium acetate was added every 4 h. At the end of this period, the alcohol was removed by distillation, and the residue was dried and dissolved in chloroform–benzene (1 : 1) and chromatographed with a column filled with aluminum oxide. Two fractions – a yellow fraction (R_f 0.9) and a violet fraction (R_f 0.5) – were collected. The solvent was removed from the violet fraction by distillation to give quinones IXa, b and XI; removal of the solvent from the yellow fraction by distillation yielded 2-acetoxy-3-chloro-1.4-naphthoquinone with mp 98-99° (from hexane) [3].

2-(1-Ethyl-2-benzimidazolylamino)-3-chloro-1,4-naphthoquinone (IXa). This compound was obtained in 43% yield as violet prisms with mp 195-196° (from o-xylene). IR spectrum: 1672 and 1658 cm^{-1} (CO). Found: C 64.8; H 4.4; Cl 9.9; N 12.0%. $C_{19}H_{14}ClN_3O_2$. Calculated: C 64.8; H 4.0; Cl 10.0; N 11.9%.

2-(1-Benzyl-2-benzimidazolylamino)-3-chloro-1,4-naphthoquinone (IXb). This compound was obtained in 40% yield as violet prisms with mp 174-175° (from o-xylene). IR spectrum: 1670 and 1660 cm^{-1} (CO). Found: C 69.7; H 3.7; Cl 8.6; N 11.6%. $C_{24}H_{16}ClN_3O_2$. Calculated: C 69.7; H 3.9; Cl 8.6; N 11.6%.

2-(4-Phenyl-2-thiazolylamino)-3-chloro-1,4-naphtoquinone (XI). This compound was obtained in 36% yield as violet prisms with mp 217-218° (from o-xylene). Found: C 62.2; H 3.4; Cl 9.5; N 7.8; S 8.5%. $C_{19}H_{11}ClN_2O_2S$. Calculated: C 62.2; H 3.0; Cl 9.7; N 7.6; S 8.7%.

5-Ethylbenzimidazo[1,2-a]naphtho[2,3-d]imidazole-7,12-dione (X) Hydrochloride. A solution of 1.3 g (3.7 mmole) of IXa in 10 ml of glacial acetic acid was refluxed for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with ether to give 0.7 g (77%) of X. IR spectrum: 1660 and 1643 cm^{-1} (CO). Found: C 64.8; H 4.4; Cl 10.2%. $C_{19}H_{13}N_3O_2 \cdot HCl$. Calculated: C 64.8; H 4.0; Cl 10.0%.

Di(2-benzothiazolyl) Disulfide. A 3.34-g (20 mmole) sample of 2-mercaptobenzothiazole was added to a hot solution of 2.14 g (10 mmole) of I in 40 ml of alcohol and 40 ml of dioxane, and the mixture was refluxed for 1 h. The initially dark-red solution became lighter, and colorless needles precipitated. The solution was cooled, and the precipitate was removed by filtration to give 1.5 g of a product with mp 182-184° (from dioxane containing alcohol). The product was insoluble in alkalis but soluble in dilute sulfuric acid. The IR spectrum did not contain the absorption bands of functional groups. The melting point was in agreement with the literature value [4], and the results of elementary analysis were in agreement with the values calculated for di(2-benzothiazolyl) disulfide. Found: C 51.0; H 2.6; N 8.7%. $C_{14}H_8N_2S_4$. Calculated: C 50.6; H 2.4; N 8.4%.

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SYNTHESIS AND PROPERTIES OF CYANOPYRROLES

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A number of cyanopyrroles were synthesized. The nitrile group was created by treatment of pyrrolecarboxylic acids with p-toluenesulfonamide and phosphorus pentachloride. It was found that the pyrrole ring is rapidly N-methylated in the presence of diazomethane when it contains three electron-acceptor substituents.

One of the most complex problems that arise in the synthesis of heme *a* – the prosthetic group of cytochromoxidase – is the introduction of a formyl group in the 8 position of the macrocycle. The preparation of porphyrins with a nitrile group and their subsequent reduction to formylporphyrins may serve as a possible approach to the solution of this problem. A recently proposed method [1] makes it possible to selectively reduce the nitrile group in the presence of vinyl and keto groups, and this is particularly valuable in the synthesis of compounds similar to heme *a*.

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