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SYNTHESIS OF 3-SUBSTITUTED 5-(3,5,6-TRICHLORO-1,4-BENZOQUINON-2-YL)THIAZOLINE-2-THIONES

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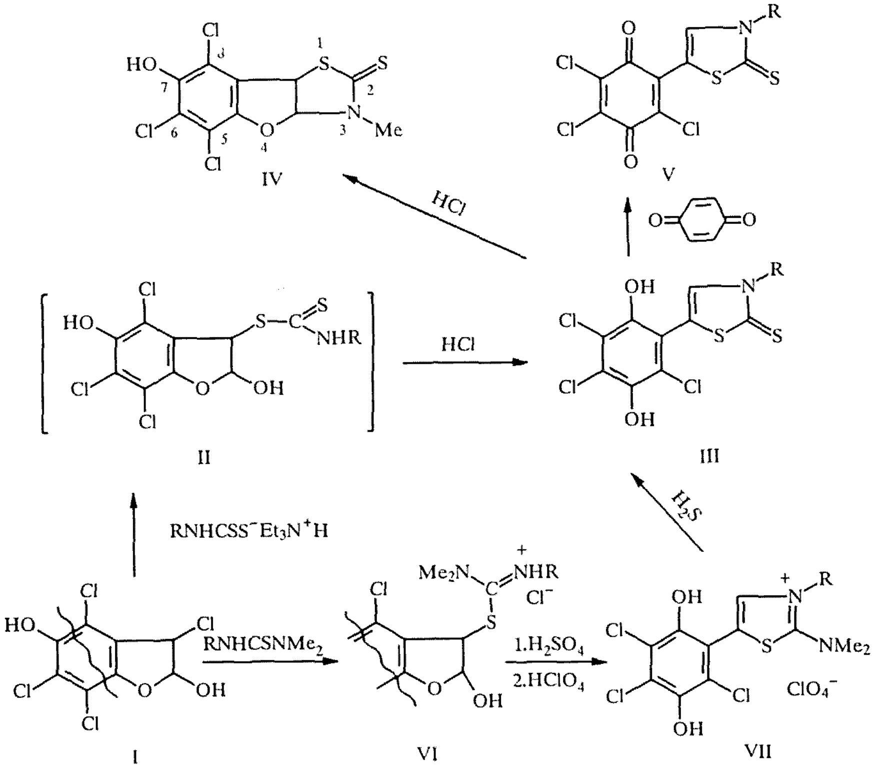
By the interaction of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with salts of N-monosubstituted dithiocarbamic acids, followed by oxidation of the resulting products by benzoquinone, 3-substituted 5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazoline-2-thiones have been obtained. An alternative method of synthesis is also proposed, including reaction of the original benzofuran with N-substituted N',N'-dimethylthioureas, cyclization of the resulting thiouronium salt to form 3-substituted 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-dimethylaminothiazolium cations, treatment of these cations with hydrogen sulfide, and subsequent oxidation of the hydroquinone fragment to quinone.

2,5-Dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan (I) [1] was proposed in one of our subsequent publications [2] as a universal synthon for obtaining trichloro-1,4-benzoquinolyl-substituted heterocycles: thiazoles [3], selenazoles [4], pyrazoles [5], and 4H-1,3,4-thiadiazines [6]. In the molecules of these compounds, we observe intramolecular charge transfer between the electron-donor heterocycle and the electron-acceptor fragment trichloro-1,4-benzoquinone, which is reflected in the electronic spectra of these compounds. In studying this phenomenon, it is of interest to synthesize those derivatives of the heterocycles that would have stronger electron-donor properties (thiazolinethiones, dithiolthiones, tetrathiafulvalenes).



For compounds II, III, and V-VII: a) R = Me, b) R = Ph.

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The work reported here was aimed at synthesizing 3-alkyl- or 3-aryl-5-(trichloro-1,4-benzoquinonyl)thiazoline-2-thiones (V) and studying their spectroscopic characteristics. In this connection, we investigated the reaction of the benzopyran I with salts of N-methyl- and N-phenyldithiocarbamic acid. For intramolecular cyclization of the intermediate product of nucleophilic substitution of chlorine (II), it was necessary to add hydrochloric acid (see analogous reactions in the review [7]), after which we observed the formation of 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methyl(or phenyl)thiazoline-2-thiones (IIIa,b).

An unexpected result was obtained in an attempt to recrystallize the hydroquinone IIIa from ethanol with added concentrated hydrochloric acid. We obtained a compound IV, isomeric in composition with IIIa, giving a PMR spectrum that did not contain the singlet at 7.7-7.8 ppm corresponding to a 4-H thiazoline ring. Instead, two doublets appeared at 5.81 and 6.93 ppm (^3J = 7 Hz). This result indicates intramolecular addition of the phenolic hydroxyl at the C=C bond of the thiazoline, forming 7-hydroxy-3-methyl-4,6,8-trichloro-2,3,3a,8b-tetrahydrothiazolo[4,5-b]benzo[d]furan-2-thione (IV). An example of intramolecular addition of phenolic hydroxyl at an enamine C=C bond was reported in [8].

The hydroquinones IIIa,b are oxidized by benzoquinone to the corresponding quinones Va,b. The quinones Va,b were recovered in the form of dark-blue crystals, poorly soluble in alcohols or benzene but readily soluble in DMF or DMSO. In their IR spectra we observed bands corresponding to C=O and C=C bonds of 1,4-benzoquinone [8]; and in the PMR spectra, we observed a singlet of the 4-H of thiazoline at 8.27-8.35 ppm. In the electronic spectra of the quinones Va,b we observed an intense absorption band at 334-336 nm, which can be assigned to a $\pi\rightarrow\pi^*$ transition in the benzoquinone system, along with a less intense band at 281-287 nm; we also observed an absorption band in the visible region at 578-580 nm due to charge transfer between the thiazoline and quinoid parts of the molecule. In comparison with 3-phenyl-2-phenylimino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazoline [2] (λ_{max} 660 nm), the charge transfer band in the spectra of the quinones Va,b is shifted hypsochromically, indicating that the 3-methyl(or phenyl)thiazoline-2-thione fragment has a lower electron-donor strength than the 3-phenyl-2-phenyliminothiazoline fragment.

We also developed an alternative method for synthesizing the quinones V, or, more precisely, for synthesizing their predecessors III. The action of N-methyl- or N-phenyl-N',N'-dimethylthiourea on the benzofuran I gives the corresponding thiouronium salts VIa,b, which are recyclized in an acidic medium to form 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-dimethylamino-3-methyl(or phenyl)thiazolium cations, isolated in the form of the perchlorates VIIa,b (see [10] for a preliminary communication). We were not able to obtain the thiazolium salt VIIa by direct methylation of the corresponding 5-aryl-2-dimethylaminothiazole, a result that can be explained by its existence in the betaine form [3]. The action of hydrogen sulfide in pyridine on the thiazolium salts VIIa,b gives the corresponding thiazolinethiones IIIa,b.

EXPERIMENTAL

IR spectra were recorded in Specord M-80 and IR-75 instruments, on suspensions in white mineral oil or hexachlorobutadiene. Electronic spectra were obtained in a Specord UV-Vis instrument, on solutions in ethanol ($c = 1.15 \times 10^{-5}$ M). PMR spectra were obtained in a WH-90/DS spectrometer with a working frequency of 90 MHz, on solutions in $CDCl_3$ or DMSO-d_6; the chemical shifts were measured relative to TMS internal standard.

The course of the reaction and the purity of the products were monitored by means of TLC on Silufol UV-254 plates (chloroform eluent).

The results of elemental analysis for C, H, Cl, N, and S matched the calculated values.

The benzofuran I was obtained by a procedure given in [1].

5-(2,5-Dihydroxy-3,4,6-trichlorophenyl)-3-methyl(or phenyl)thiazoline-2-thiones (IIIa, $C_{10}H_6Cl_3NO_2S_2$; (IIIb, $C_{14}H_8Cl_3NO_2S_2$). A. To a solution of 0.87 g (3 mmoles) of the benzofuran I in 20 ml of ethanol, there was added 3 mmoles of the triethylammonium salt of N-methyl- or N-phenyldithiocarbamic acid. The mixture was refluxed for 2 h, after which 5 ml of concentrated hydrochloric acid was added, and the heating was continued for 2 h. The reaction mixture was cooled and poured into 100 ml of a 5% aqueous solution of sodium acetate. The crystals were separated, washed with water, and vacuum-dried. Yield of IIIa 83%, IIIb 81%.

B. A 2-mmole quantity of the perchlorate VIIa or VIIb was suspended in 15 ml of pyridine, and hydrogen sulfide was bubbled through the suspension until a transparent solution was formed (~10 min). Then the solution was diluted with 10 ml of water, and the precipitate was separated and washed on the filter with 5% aqueous hydrochloric acid, then water, and vacuum-dried. Yield of IIIa 72%, IIIb 76%.

IIIa, mp 182-184°C (decomp., 1:4 ethanol–carbon tetrachloride). IR spectrum, cm^{-1}: 3264 (OH), 1642, 1632, 1578, 1558. PMR spectrum (DMSO-d_6), ppm: 9.97 (1H, s, OH); 9.84 (1H, s, OH); 7.70 (1H, s, C_4-H thiazoline); 3.65 (3H, s, CH_3). R_f 0.14.

IIIb, mp 176-180°C (decomp., carbon tetrachloride). IR spectrum, cm^{-1}: 3348 (OH), 2972, 1606, 1566, 1558, 1496. PMR spectrum (DMSO-d_6), ppm: 9.96 (2H, s, OH); 7.79 (1H, s, C_4-H thiazoline); 7.54 (5H, m, C_6H_5). R_f 0.18.

7-Hydroxy-3-methyl-4,6,8-trichloro-2,3,3a,8b-tetrahydrothiazolo[4,5-b]benzo[d]furan-2-thione (IV, $C_{10}H_6Cl_3NO_2S_2$). A 0.7-g quantity (2 mmoles) of compound IIIa was dissolved with heating in 15 ml of ethanol, diluted with 4 ml of concentrated hydrochloric acid, and held for 48 h in a refrigerator. The slightly yellowish crystals that were formed were filtered off, washed on the filter with ethanol, and air-dried. Yield 31%, mp 198-201°C. IR spectrum, cm^{-1}: 3320 (OH), 1640, 1576, 1532. PMR spectrum (DMSO-d_6), ppm (and J, Hz): 10.4 (1H, s, OH); 6.93 (1H, d, C_2-H, $^3J = 7$ Hz); 5.81 (1H, d, C_3-H, $^3J = 7$ Hz); 2.48 (3H, s, CH_3). R_f 0.37.

3-Methyl(or phenyl)-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazoline-2-thiones (Va, $C_{10}H_4Cl_3NO_2S_2$; Vb, $C_{14}H_6Cl_3NO_2S_2$). A 1-mmole quantity of the hydroquinone IIIa or IIIb was dissolved in 10 ml of ethanol, 0.16 g (1.5 mmoles) of benzoquinone was added, and the mixture was stirred for 1 h at 20°C. The dark-blue crystals were separated and air-dried. Yield of Va 72%, Vb 83%.

Va, mp 214-215°C (methanol). IR spectrum, cm^{-1}: 3136, 2940, 1702 (C=O), 1670 (C=O), 1610, 1598, 1554, 1542, 1510. PMR spectrum ($CDCl_3$): 8.27 (1H, s, C_4-H thiazoline); 3.76 (3H, s, CH_3). UV spectrum (ethanol), λ_{max}, nm (and log ε): 281 (4.09), 334 (4.15), 578 (3.5). R_f 0.47.

Vb, mp 232-234°C (2-propanol). IR spectrum, cm^{-1}: 2944, 1721 (C=O), 1697 (C=O), 1680 (C=O), 1670 (C=O), 1606, 1561, 1541, 1525, 1494. PMR spectrum ($CDCl_3$), ppm: 8.35 (1H, s, C_4-H thiazoline); 7.54 (5H, m, C_6H_5). UV spectrum (ethanol), λ_{max}, nm (and log ε): 287 (4.16), 336 (4.08), 580 (3.44). R_f 0.57.

Hydrochlorides of 2,5-Dihydroxy-3-(N,N-dimethyl-N′-methyl(or phenyl)isothioureido-4,6,7-trichloro-2,3-dihydrobenzo[b]furans (VIa, $C_{12}H_{14}Cl_4N_2O_2S$; VIb, $C_{17}H_{16}Cl_4N_2O_2S$). A mixture of 0.87 g (3 mmoles) of the benzofuran I, 3 mmoles of the thiourea, and 10 ml of acetone was stirred for 1 h at 20°C, after which the mixture was refluxed for 1 h. The crystals that precipitated upon cooling were filtered and washed on the filter with a small quantity of ethanol. Yield of VIa 87%, VIb 74%.

VIa, mp 172-173°C (aqueous ethanol). IR spectrum, cm^{-1}: 3392, 3272, 1632, 1408. PMR spectrum (DMSO-d_6), ppm (and J, Hz): 10.2 (2H, s, OH); 5.66 (1H, d, C_2-H, $^3J = 3$ Hz); 5.30 (1H, d, C_3-H, $^3J = 3$ Hz); 3.44 (3H, s, CH_3); 3.35 (6H, s, $2CH_3$) .

VIb, mp 178-179°C (ethanol). IR spectrum, cm^{-1}: 3389, 3088, 1618, 1590, 1564, 1494. PMR spectrum (DMSO-d_6), ppm (and J, Hz): 10.20 (1H, s, OH); 10.11 (1H, s, OH); 7.56 (5H, m, C_6H_5); 5.80 (1H, d, C_2-H, $^3J = 3$ Hz); 5.49 (1H, d, C_3-H, $^3J = 3$ Hz); 3.55 (6H, s, $2CH_3$).

5-(2,5-Dihydroxy-3,4,6-trichlorophenyl)-2-dimethylamino-3-methyl(or phenyl)thiazolium Perchlorates (VIIa, $C_{12}H_{12}Cl_4N_2O_6S$; VIIb, $C_{16}H_{14}Cl_4N_2O_6S$). A solution of 2 mmoles of the isothiouronium salt VIa or VIb in 3 ml of concentrated sulfuric acid was held for 1 h at 60°C. After cooling, 5 ml of 75% perchloric acid was added, and the mixture was poured onto 50 g of ice. The colorless crystals that precipitated were filtered, washed on the filter with cold water, and dried at 50°C. Yield of VIIa 89%, VIIb 83%.

VIIa, mp 192-196°C (decomp., water). IR spectrum, cm^{-1}: 3352, 3096, 1608, 1540. PMR spectrum (DMSO-d_6), ppm: 10.10 (2H, s, OH); 7.72 (1H, s, C_4-H thiazolium); 3.94 (3H, s, CH_3); 3.35 (6H, s, $2CH_3$).

VIIb, mp 182-185°C (decomp., water). IR spectrum, cm^{-1}: 3572 (OH), 3320 (OH), 3092, 1628, 1610, 1588, 1540, 1492. PMR spectrum (DMSO-d_6), ppm: 10.10 (2H, s, OH); 7.81 (1H, s, C_4-H thiazolium); 7.58 (5H, m, C_6H_5); 3.47 (6H, s, $2CH_3$).

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