SYNTHESIS OF TRICHLORO-1,4-BENZOQUINONYL-SUBSTITUTED 2,2'-BITHIAZOLES

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2,2'-Bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazole] and 6-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2imino-3,4-dihydro-4H-1,4-thiazin-3-thione are synthesized from 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3dihydrobenzo[b]furan and dithiooxalyldiamide. The products are oxidized by FeCl₃ to the corresponding trichloro-1,4-benzoquinonyl-substituted sulfur-containing heterocycles. N-Methylation of 2,2'-bithiazole by dimethyl sulfate gives 2,2'-bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methylthiazolium] bismonomethyl sulfate. The last compound is readily transformed to 2,2'-bi[5-(2-hydroxy-5-oxido-3,4,6trichlorophenyl)-3-methylthiazolium] bisbetaine.

We have developed a method of synthesis [1, 2] of trichloro-1,4-benzoquinonyl-substituted heterocycles based on the common precursor (synthon) 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan (I) [3]. The synthesis is based on recyclization of the compound I with various bifunctional sulfur-containing nucleophiles and subsequent oxidation of the hydroquinone moiety in the final products. In the molecule of the synthesized benzoquinonyl-substituted heterocycles intramolecular charge transfer (the electron-donating heterocycle is bonded through a C–C bond to the electron-withdrawing benzoquinone fragment), occurs being reflected in their electronic spectra.

The aim of the present work is to synthesize 2-2'-bithiazole, which is bonded through carbon-carbon bonds to two trichloro-1,4-benzoquinone residues, and to investigate the possibility of transforming it to the dithiadiazafulvalene derivatives. Bi(1,3-thiazolin-2)ylidenes (dithiadiazafulvalenes) and the corresponding thiazolium carbenes are of both chemical and biological interest as possible intermediates in the deprotonation of thiazolium salts [4]. Recently dithiadiazafulvalenes have been recognized as strong electron-donors - potential components for synthesizing electroconducting ion-radical salts [5, 6].

Reaction of benzofuran I with dithiooxalyldiamide in boiling CH₃CN produces an easily separable mixture of 2,2'-bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazole] (II) and 6-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2imino-3,4-dihydro-4H-1,4-thiazin-3-thione (III). The yields are 46 and 28%, respectively. We increased the yield of 2,2'-bithiazole by carrying out the reaction in acetic acid or toluene and simultaneously changing the ratio of the reagents (see Experimental). The yield of 2,2'-bithiazole II in this instance reaches 61%. Thiazine III in this instance is formed in smaller quantities and was not isolated. The hydroquinone moiety in compounds II and III is readily oxidized by FeCl₃ to the benzoquinone fragment to give the corresponding trichloro-1,4-benzoquinonyl-substituted heterocycles - 2,2'-bi[5-(trichloro-1,4-benzoquinonyl)thiazole] (IV) and 2-imino-6-(trichloro-1,4-benzoquinonyl)-3,4-dihydro-4H-1,4-thiazin-3-thione (V). Acetylation of compounds II and III by acetic anhydride in the presence of orthophosphoric acid gives 2,2'-bi[5-(2,5-diacetoxy-3,4,6-trichlorophenyl)thiazole] (VI) and 2-acetylimino-6-(2,5-diacetoxy-3,4,6-trichlorophenyl)-3,4-dihydro-4H-1,4-thiazin-3-thione (VII), respectively.

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The PMR spectrum of 2,2'-bithiazole II contains a singlet of the 4-H proton of the thiazole ring and two broadened signals of the OH protons. The ratio of intensities of these signals is consistent with the symmetric structure of the II molecule. The spectrum of thiazine III contains a singlet for the 5-H proton and four broadened

signals for the OH and NH protons.

The UV spectrum of quinone IV exhibits two strong absorption maxima at 303 and 355 nm. These correspond to the $\pi \rightarrow \pi^*$ transition in the benzoquinone and thiazole systems. The spectrum also contains an intramolecular charge transfer band at 525 nm. The intramolecular charge transfer band in the UV spectrum of quinone V is shifted hypsochromically in comparison with the corresponding band in spectra of trichloro-1,4-benzoquinonyl-substituted thiazoles [7].

The spectroscopic characteristics of acetyl derivatives VI and VII (see Experimental) are good evidence not only of their structures but also of the structure of the precursors II and III.

We attempted reductive methylation of 2,2'-bithiazole II by formaldehyde and formic acid in order to prepare the methyl derivative of dithiadiazafulvalene bonded with two trichlorohydroquinone moieties. However, we were unsuccessful in preparing the desired product VIII. Methylation of the nitrogen atom of the thiazole ring was effected by heating of 2,2'-bithiazole II with dimethyl sulfate. The product was 2,2'-bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methylthiazolium] bismonomethyl sulfate (IXa). Compound IXa was transformed by perchloric acid into the corresponding diperchlorate IXb. Both salts IXa and IXb are stable only in acidic aqueous medium. In neutral solutions they hydrolyze to 2,2'-di[5-(2-hydroxy-5-oxido-3,4,6-trichlorophenyl)-3-methylthiazolium] bisbetaine (X). Treatment of bisbetaine X with perchloric acid again converts it to the diperchlorate IXb. Attempts to oxidize the hydroquinone residues in compound X to benzoquinone moieties by using FeCh, Cr(VI) oxide, potassium dichromate, or nitrogen oxides were not successful owing to more extensive oxidation processes.

Compounds IXa,b and X are difficultly soluble in most organic solvents except for the aprotic dipolar solvents DMF and DMSO.

The PMR spectrum of bismonomethyl sulfate IXa contains singlets of the methyl group protons both of the methyl sulfate anion and the quaternized nitrogen atom of the thiazole ring (see also [4]), a broad signal of the OH group, and a singlet of the 4-H proton of the thiazole ring. The spectrum of diperchlorate IXb has a singlet of the

methyl groups on the quaternized nitrogen atom, a broad signal of the OH group, and a singlet of the 4-H proton. The PMR spectrum of bisbetaine is practically identical. Bisbetaine X is intensely deep violet. Its UV spectrum in ethanol has two strong absorption maxima assigned to $\pi \rightarrow \pi^*$ transitions and a strong maximum at 541 nm.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument for suspensions in nujol (1900-1500 cm⁻¹, NaCl prism) or in hexachlorobutadiene (3800-2000 cm⁻¹, LiF prism) and for saturated solutions in dioxane. Electronic spectra were recorded on a Specord M-40 instrument for chloroform or ethanol solutions (concentration 10^{5} -5 $\cdot 10^{-5}$ M). PMR spectra were obtained on a Bruker H-90 (90 MHz) instrument using CDCl₃ or DMSO-d₆ as solvent and TMS as internal standard.

The purity of the compounds was monitored using TLC on Silufol UV-254 silica gel plates and ethyl acetate–CCl₄ or ethyl acetate–CCl₄–ethanol eluent. Visualization was carried out by UV light and iodine.

2,5-Dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan (I) was prepared by the literature method [3].

2,2'-Bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazole] (II) and 6-(2,5-Dihydroxy-3,4,6-trichlorophenyl)-2-imino-3,4-dihydro-4H-1,4-thiazin-3-thione (III). A. Mixture of benzofuran I (2.6 g, 9 mmol), rubeanic acid (1.07 g, 8.9 mmol), and anhydrous acetonitrile (70 ml) was boiled for 4 h. The starting materials dissolved during the course of the reaction. Then a precipitate formed. The hot solution was filtered to give a greenish-yellow solid (II). The solid was purified by heating several minutes in acetonitrile (20-25 ml) and filtering the hot solution. Yield 1.2 g (46%) of compound II; mp 330°C (dec.). IR spectrum: 3486, 3362, 1598, 1562 cm⁻¹. PMR spectrum (DMSO-d₆): 8.02 (2H, s, 2-H); 9.87 (2H, s, 20H); 10.04 ppm (2H, s, 20H). Found, %: C 36.43; H 1.47; Cl 35.36; N 4.57; S 10.73. C₁₈H₆Cl₆N₂O₄S₂. Calculated, %: C 36.57; H 1.02; Cl 35.99; N 4.74; S 10.85.

The combined filtrate after separating and purifying of compound II was held for 20 h at 0°C. The resulting yellow solid (III) was filtered off. Yield 0.9 g (28%). After recrystallization from acetonitrile, mp >240°C (dec.). IR spectrum: 3520, 3408, 3305, 3276, 3168, 2948, 1634, 1562, 1504 cm⁻¹. PMR spectrum (DMSO-d₆): 7.93 (1H, s, 5-H); 9.69 (1H, s, NH); 9.78 (1H, s, OH); 9.96 (1H, s, NH); 10.08 ppm (1H, s, OH). Found, %: C 33.45; H 1.11; Cl 29.34; N 8.04; S 18.05. $C_{10}H_5Cl_3N_2O_2S_2$. Calculated, %: C 33.77; H 1.42; Cl 29.91; N 7.88; S 18.03.

B. Mixture of benzofuran I (0.58 g, 2 mmol), rubeanic acid (0.12 g, 1 mmol), and glacial acetic acid (8 ml) was boiled for 3 h. The precipitate that formed after cooling to 20° C was filtered off and washed with hot acetonitrile (20 ml). Yield 0.36 g (61%) of the compound II.

C. Mixture of benzofuran I (0.44 g, 1.5 mmol), rubeanic acid (0.06 g, 0.5 mmol), and toluene (7 ml) was boiled for 3 h. The dark solution was filtered hot, the precipitate was washed with toluene and hexane, boiled in acetonitrile (10-15 ml) for 2-3 min, and filtered off. Yield 0.18 g (61%) of the compound II.

Samples of compound II obtained by methods A, B, and C were identical according to IR and PMR spectra.

2,2'-Bi[5-(trichloro-1,4-benzoquinonyl)thiazole] (IV). Solution of the compound II (0.4 g, 0.68 mmol) in DMF (8 ml) was treated with vigorous stirring (magnetic stirrer) at 20°C over 2-3 min dropwise with aqueous FeCl₃ (20%, 16 ml). The reaction mixture was stirred intensely at the same temperature for an additional 2 h and was left for 24 h. The precipitate was separated, washed with water, and dried. Yield 0.36 g (90%) of violet crystals of compound IV; mp 310°C (dec.). The product was recrystallized from toluene; mp 312°C (dec.). IR spectrum: 1682 and 1670 (C=O quinone), 1570 cm⁻¹ (C=C quinone). UV spectrum (CHCl₃, $c = 5 \cdot 10^{-5}$ M) (log ε): 303 (4.56), 355 (4.58), 525 nm (4.13). PMR spectrum (DMSO-d₆): 8.65 ppm (s, 4-H). Found, %: C 37.10; H 0.57; Cl 35.98; N 4.92; S 11.14. C₁₈H₂Cl₆N₂O₄S₂. Calculated, %: C 36.82; H 0.34; Cl 36.24; N 4.77; S 10.92.

2-Imino-6-(trichloro-1,4-benzoquinonyl)-3,4-dihydro-4H-1,4-thiazin-3-thione (V). Oxidation of compound III (0.30 g, 0.84 mmol) in DMF (4 ml) using aqueous FeCl₃ (20%, 16 ml) by the method described above yielded 0.28 g (94%) of dark red fine crystals of compound V that were recrystallized from anhydrous benzene; mp 180°C (dec.). IR spectrum: 3304 (NH), 3280, 3176 (NH), 1684 and 1670 (C=O quinone), 1646 (C=N), 1640, 1608, 1570 cm⁻¹ (C=C quinone). UV spectrum (CHCl₃, $c = 2.5 \cdot 10^{-5}$ M) (log ε): 297 (4.25), 334 (4.22), 471 nm (3.59). PMR spectrum (DMSO-d₆): 8.40 (1H, s, 5-H); 9.93 (1H, s, NH); 10.27 ppm (1H, s, NH). Found, %: C 39.70; H 1.03; Cl 29.58; N 8.10; S 18.01. C₁₀H₃Cl₃N₂O₂S. Calculated, %: C 39.96; H 0.86; Cl 30.08; N 7.92; S 18.13.

2,2'-Bi[5-(2,5-diacetoxy-3,4,6-trichlorophenyl)thiazole] (VI). Mixture of the compound II (0.2 g, 0.34 mmol), acetic anhydride (6 ml), and orthophosphoric acid (5 drops) was held at 100°C for 2 h. During the heating II completely dissolved. Then a light-colored precipitate formed. The reaction mixture was cooled. The precipitate was filtered off, washed with a small amount of acetic acid and water, and dried. Yield 0.26 g (99%) of tetraacetate VI as colorless crystals; mp 275-277°C. IR spectrum: 2490, 1778 (C=O) cm⁻¹ (in nujol); 1790 (C=O) cm⁻¹ (in dioxane). PMR spectrum (CDCl₃): 2.21 (6H, s, 2CH₃); 2.44 (6H, s, 2CH₃); 7.85 ppm (2H, s, 4-H). Found, %: C 40.88; H 1.95; Cl 27.46; N 3.53; S 8.16. $C_{26}H_{14}Cl_6N_2O_8S_2$. Calculated, %: C 41.13; H 1.86; Cl 28.02; N 3.69; S 8.47.

2-Acetylimino-6-(2,5-diacetoxy-3,4,6-trichlorophenyl)-3,4-dihydro-4H-1,4-thiazin-3-thione (VII). Mixture of the compound III (0.30 g, 0.84 mmol), acetic anhydride (6 ml), and orthophosphoric acid (5 drops) was held at 50-70°C for 0.5 h. The resulting warm solution was filtered. The filtrate was treated with several drops of ethanol and held at 0°C for 24 h. The precipitate formed was separated, washed successively with ethanol and diethyl ether, and dried. Yield 0.2 g, (50%) of rose-colored crystals; mp 172-174°C. Recrystallization from ethanol yielded colorless crystals of the compound VII; mp 175-176°C. IR spectrum: 3272 (narrow band, NH), 2924, 1774 (CH₃COO), 1714 cm⁻¹ (CH₃CON) (in nujol); 1790 (CH₃COO), 1724 cm⁻¹ (CH₃CON) (in dioxane). PMR spectrum (CDCl₃): 2.12 (3H, s, CH₃COO); 2.35 (3H, s, CH₃COO); 2.55 (3H, s, CH₃CON); 7.76 (1H, s, 5-H); 10.90 ppm (1H, s, NH). Found, %: C 39.64; H 2.12; Cl 22.42; N 5.53; S 13.09. C₁₆H₁₁Cl₃N₂O₅S₂. Calculated, %: C 39.89; H 2.30; Cl 22.08; N 5.82; S 13.31.

2,2'-Bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methylthiazolium] Bismonomethyl Sulfate (IXa). Mixture of the compound II (0.3 g, 0.5 mmol) and dimethyl sulfate (5 ml) was held at 120-130°C for 2 h. The cooled reaction mixture was treated with anhydrous ethanol (5 ml), anhydrous ether (20 ml), and held at 0°C for 12 h. The precipitate formed was separated, washed with anhydrous ether, and dried in a desiccator. Yield 0.35 g (83%) of orange crystals of the compound IXa; mp >280°C (dec.). IR spectrum: 3400-3300 (br., OH), 2950, 1655, 1552 cm⁻¹. PMR spectrum (DMSO-d₆): 3.38 (6H, s, 2CH₃O); 4.27 (6H, s, 2CH₃N⁺); 5.60 (4H, br. s, 4OH); 9.35 ppm (2H, s, 4-H). Found, %: C 31.14; H 2.30; Cl 24.60; N 3.11; S 15.99. C₂₂H₁₈Cl₆N₂O₁₂S₄. Calculated, %: C 31.33; H 2.15; Cl 25.22; N 3.32; S 15.21.

2,2'-Bi[5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methylthiazolium] Diperchlorate (IXb). Solution of the compound IXa (0.25 g, 0.3 mmol) in anhydrous ethanol (25 ml) was treated with perchloric acid (70%, 2 ml). The reaction mixture was held at 0°C for 12 h. The precipitate was separated, successively washed with anhydrous ethanol and anhydrous ether, and dried. Yield 0.17 g (70%) of yellow crystals of the compound IXb; mp >260°C (dec.). IR spectrum: 3390 (br., OH), 1650, 1553 cm⁻¹. PMR spectrum (DMSO-d₆): 3.80 (br. s, OH + H₂O); 4.22 (6H, s, 2CH₃N⁺); 9.33 ppm (2H, s, 4-H). Found, %: C 29.54; H 1.33; Cl 34.29; N 3.24; S 8.00. C₂₀H₁₂Cl₈N₂O₁₂S₂. Calculated, %: C 29.29; H 1.47; Cl 34.59; N 3.42; S 7.82.

2,2'-Bi[5-(2-hydroxy-5-oxido-3,4,6-trichlorophenyl)-3-methylthiazolium] Bisbetaine (X). A. Suspension of the compound IXa (0.17 g, 0.2 mmol) in distilled water (15 ml) was heated to boiling. The precipitate was immediately filtered off, washed with distilled water, and dried. Yield 0.12 g (97%) of dark violet crystals of the compound X; mp >300°C (dec.). IR spectrum: 3330 (br., OH), 3160, 2956, 1572, 1534, 1508 cm⁻¹. UV spectrum (ethanol, $c = 10^{-5}$ M) (log ε): 232 (4.51), 368 (4.17), 541 nm (4.15). PMR spectrum (DMSO-d_6): 4.10 (br. s, OH + H₂O); 4.23 (6H, s, 2CH₃N⁺); 9.35 ppm (2H, s, 4-H). Found, %: C 39.01; H 1.48; Cl 33.85; N 4.41; S 10.70. C₂₀H₁₀Cl₆N₂O₄S₂. Calculated, %: C 38.79; H 1.63; Cl 34.36; N 4.52; S 10.36.

B. Method A using compound IXb (0.16 g, 0.2 mmol) produced 0.11 g (92%) of dark violet crystals of the compound X; mp >300°C (dec.). The spectral properties of samples of X prepared by methods A and B are identical.

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