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## BIS(2-CHLOROSULFONYLPHENYL) DISELENIDE - THE SUBSTRATE FOR ORGANOSELENIUM SULFONAMIDES

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Abstract: Synthesis of bis(2-chlorosulfonylphenyl) diselenide (11) from 2-aminobenzenesulfonic acid was elaborated. It was shown that (11) is a good starting material for synthesis of the organoselenium sulfonamides, such as bis(2-sulfamoylphenyl) diselenides (3) and benz-2,3-azaselenathiophene 1,1-dioxides (4), being potential immunostimulants and oxidation catalysts.

Bis(2-carbamoylphenyl) diselenides (1) and 1,2-benzisoselenazol-3(2H)-ones (2), having carboxamide function as a substituent or as moiety of the heterocyclic ring, have been a subject of current interest as antioxidants and antiinflammatory agents. A broad spectrum of their biological activity has been recently reviewed.<sup>1,2</sup> In our previous works, some of these compounds have been reported as modest immunostimulants able to induce cytokines (IFN, TNF, IL-2) in the human peripheral blood leukocytes.<sup>3-6</sup> They have also been found as inhibitors of the constitutive endothelial nitric oxide synthase - the enzyme response for the endothelium-dependent vasorelaxation.<sup>6,7</sup> Moreover, it has been revealed that

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some of diselenides 1 and benzisoselenazolones 2 exhibit strong catalytical effects in hydrogen peroxide oxidation of various organic compounds.<sup>8</sup>

In this work, we present synthesis of two representatives of the compounds **3** and **4** being the analogs of **1** and **2** containing the sulfonyl group instead of the carbonyl one. Since the key substrate for them is bis[(chlorosulfonyl)phenyl] diselenide (**11**), the method for its synthesis had to be elaborated. Moreover, we present the synthesis of 2-(chloroseleno)- and 2-(bromoseleno)benzenesulfonyl chloride (**8** and **12**), being the expected substrates for synthesis of benz-2,3-azaselenathiophene 1,1-dioxides (**4**).



The starting material was 2-aminobenzenesulfonic acid (5) which was converted into the sodium salt, treated with sodium nitrite to produce internal diazonium salt (6). The salt 6 reacted with aqueous potassium selenocyanate giving 2-(cyanoseleno)benzenesulfonate (7). In the alkaline medium it was converted into the mixture of the seleninic acid (9) and diselenide (10). The mixture was treated with hydrazine which reduced seleninic acid (9) to the diselenide (10) which finally was obtained as a sole product. In the next step of the synthesis, bis(2--chlorosulfonylphenyl) diselenide (11) was obtained by conversion of the sulfonyl group in the compound (10) into chlorosulfonyl group with phosphorus pentachloride.

Potassium 2-(cyanoseleno)benzenesulfonate (7) heated with phosphorus pentachloride produced unstable 2-(chloroseleno)benzenesulfonyl chloride (8)



i = 1. Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O; 2. NaNO<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, -10<sup>o</sup>C ii = KSeCN, H<sub>2</sub>O, O<sup>o</sup>C iii = PCl<sub>5</sub>, 150<sup>o</sup>C iv = 1. H<sub>2</sub>O; 2. KOH, pH~12 v = H<sub>2</sub>N-NH<sub>2</sub>· H<sub>2</sub>O, 20<sup>o</sup>C vi = Br<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -10<sup>o</sup>C vii = CH<sub>3</sub>NH<sub>2</sub> (excess), C<sub>2</sub>H<sub>5</sub>OH, CH<sub>3</sub>CN, 20<sup>o</sup>C viii = (PhC(O)O<sub>2</sub>, benzene, reflux which decomposed to diselenide (11) and could not be used as a substrate for the reaction with primary amine. More convenient substrate for this reaction was stable 2-(bromoseleno)benzenesulfonyl chloride (12), easily obtained from diselenide 11 and bromine in dichloromethane. Unfortunately, its reaction with methylamine led to complex mixture of several unidentified compounds. Among them, expected 2-methylbenz-2,3-azaselenathiophene was identified by TLC but it could not be isolated. Nevertheless, this compound (having new, unique heterocyclic system with Se, S and N atoms) was smoothly obtained in a two-step way via bis(methylsulfamoylphenyl) diselenide (3a) by its oxidation with benzoyl peroxide.

### Experimental

Melting points: Digital Melting Point Apparatus Electrothermal IA 9100. <sup>1</sup>H-NMR spectra were recorded on a Bruker 300 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer 2000 FT spectrometer. All starting materials were purchased from Aldrich Chem. Co. and Fluka.

**Diazoniumbenzenesulfonate (6)**. The solution of sodium nitrite (3.45 g, 0.05 mol) in water (10 ml) was added at temperature 0°C to the solution of 2-aminobenzenesulfonic acid (95%, 8.66 g, 0,05 mol) and sodium carbonate (2.65 g, 0.025 mol) in water (50 ml). Thus prepared substrate was added dropwise into the stirred solution of sulfuric acid (98%, 19.6 g, 0.05 mol) in water (40 ml) at temperature -10°C (ice/salt bath) and the reaction was continued for additional 30 min. The crystalline salt (6) was filtered off, washed with cold water (10 ml), acetone (10 ml) and dried in the air. Pale cream-yellow prisms. Yield 8.00 g

(91%); mp 119°C (with explosion),  $v_{max}$  (KBr) cm<sup>-1</sup> 2294 (N<sub>2</sub><sup>+</sup>), 1241, 1063 (SO<sub>3</sub><sup>-</sup>). <sup>1</sup>H-NMR (DMSO):  $\delta$  7.93 (t, 1H, J=7.9 Hz, ArH), 8.03 (d, 1H, J=7.9 Hz, ArH), 8.21 (t, 1H, J=7.7 Hz, ArH), 8.69 (d, 1H, J=8.2 Hz, ArH).

**Potassium 2-(cyanoseleno)benzenesulfonate (7)**. The solution of potassium selenocyanate (7.9 g, 0.05 mol) in water (50 ml), cooled to 0°C, was added dropwise at the same temperature to a stirred suspension of diazonium salt (6) (9.2 g, 0.05 mol) in water (700 ml) during 1 h, and the reaction was continued for additional 4 h until nitrogen evolving finished. The mixture was filtered and from the filtrate water was evaporated in vacuo. The tarry residue was treated with acetone (5x200 ml) and the combined extracts were evaporated in vacuo. The solid residue was recrystallized from acetone - ethyl ether (3:2) giving product 7 as pale yellow prisms. Yield 11.65 g (78%); mp 190-192°C (with decomp.),  $v_{max}$  (KBr) cm<sup>-1</sup> 2079 (CN), 1232, 1189, 1061 (SO<sub>3</sub><sup>-</sup>). <sup>1</sup>H-NMR (DMSO):  $\delta$  7.39-7.45 (m, 2H), 7.70-7.74 (m, 2H).<sup>9</sup>

**2-(Chloroseleno)benzenesulfonyl chloride (8)**. The finely powdered reagents: potassium 2-(cyanoseleno)benzenesulfonate (7) (3.0 g, 0.01 mol) and phosphorus pentachloride (6.24 g, 0.03 mol) were heated under reflux for 1 h on the oil bath of temperature 150°C. After this period the mixture was cooled to 80°C, benzene (40 ml) was added and it was refluxed for 3 h. The hot mixture was filtered, the precipitate was washed with several portions of hot benzene and the combined filtrates were evaporated in vacuo. The liquid residue was dissolved in hexane (50 ml), decolorized with active carbon and the solvent was evaporated again. The

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product 8 was unstable red liquid which decomposed into diselenide 11 and could not be purified by chromatography or distillation. Yield 2.64 g (90%);  $v_{max}$  (film) cm<sup>-1</sup> 1371, 1162 (SO<sub>2</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.53 (t, 1H, J=7.6 Hz, ArH), 7.79 (t, 1H, J=7.7 Hz, ArH), 8.00 (d, 1H, J=8.2 Hz, ArH), 8.07 (d, 1H, J=8.0 Hz, ArH).

**Bis(2-sulfonylphenyl) diselenide dipotassium salt (10)**. The orange coloured solution of selenocyanate (7) (15 g, 0.05 mol) in water (100 ml) was adjusted to pH~12 by adding potassium-hydroxide pellets (0.28 g, 0.005 mol), and it was stirred during 30 min. at room temperature. After this period, the solution of hydrazine hydrate (0.69 g, 0.014 mol) in water (5 ml) was added and the stirring mixture was left to stand overnight (as nitrogen evolving finished). Water was evaporated in vacuo and from the residue crude product **10** was extracted with hot methanol (3x100 ml). The combined extracts were filtered, methanol was evaporated in vacuo, acetone (150 ml) was added to the residue, the mixture was stirred at room temperature for 5 h. Pure diselenide (**10**) was filtered off, dried in air and then in the dryer at 130-140°C. Pale yellow-brown powder. Yield 11.6 g (84%); decomp. above 200°C,  $v_{max}$  (KBr) cm<sup>-1</sup> 1194, 1058 (SO<sub>3</sub><sup>-</sup>). <sup>1</sup>H-NMR (DMSO):  $\delta$  7.18 (dd, 4H, J=6.1 and 3.3 Hz, ArH), 7.60 (dd, 2H, J=5.7 and 3.3 Hz ArH), 7.69 (dd, 2H, J=5.7 and 3.3 Hz, ArH).

**Bis(2-chlorosulfonylphenyl) diselenide (11)**. The finely powdered reagents: anhydrous diselenide **10** (10.94 g, 0.02 mol) and phosphorus pentachloride (12.5 g 0.06 mol) were heated under reflux for 1 h on the oil bath at 150°C. Then the mixture was cooled to  $80^{\circ}$ C, benzene (40 ml) was added and it was refluxed for

3 h, filtered while hot and the filter cake was washed with several portions of hot benzene (~100 ml). From the combined filtrates benzene was evaporated in vacuo, the tarry residue was dissolved in small wolume of dichloromethane and chromatographed on the silica gel column using dichloromethane as an eluent. The yellow coloured fraction was collected, solvent was evaporated in vacuo and the residue recrystallized from acetonitrile gave pure diselenide (11). Pale yellow flakes. Yield 7.23 g (71%); mp 157-158°C (with decomp.),  $v_{max}$  (KBr) cm<sup>-1</sup> 1360, 1173 (SO<sub>2</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.47 (td, 2H, J=7.7 and 1.2 Hz, ArH), 7.57 (td, 2H, J=7.7 and 1.5 Hz, ArH), 8.03 (dd, 2H, J=7.9 and 1.2 Hz, ArH), 8.09 (dd, 2H, J=7.9 and 1.5 Hz, ArH). Found: C, 28.16; H, 1.85; Cl, 14.11; S, 12.56. C<sub>12</sub>H<sub>8</sub>Cl<sub>2</sub>O<sub>4</sub>S<sub>2</sub>Se<sub>2</sub> (509.13) requires C, 28.31; H, 1.58; Cl, 13.93; S, 12.59.

**2-(Bromoseleno)benzenesulfonyl chloride (12)**. The solution of bromine (1.34 g, 0.0084 mol) in dichloromethane (40 ml) was added dropwise to the cooled, stirred solution of the diselenide **11** (4.07 g, 0.008 mol) in dichloromethane during 1 h period and the reaction was continued at the same temperature  $-10^{\circ}$ C for additional 3 h. The solvent was evaporated in vacuo from the water bath at 30°C and the oily residue was recrystallized from hexane (70 ml). Red prisms. Yield (5.0 g, 93%); mp 40-41°C,  $v_{max}$  (film) cm<sup>-1</sup> 1365, 1172 (SO<sub>2</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.51 (td, 1H, J=7.6 and 1.0 Hz, ArH), 7.70 (td, 1H, J=7.8 and 1.4 Hz, ArH), 8.03 (dd, 1H, J=7.6 and 1.4 Hz, ArH), 8.05 (dd, 1H, J=7.9 and 1.0 Hz, ArH).<sup>9</sup>

Bis[2-(methylsulfamoyl)phenyl] diselenide (3a). The solution of diselenide 11 in anhydrous acetonitrile was added dropwise under vigorous stirring to a 33%

solution of methylamine in methanol (Fluka) (9.3 ml, 0.075 mol) dissolved in anhydrous acetonitrile (25 ml). The reaction was carried out at  $-10^{\circ}$ C, and then continued for additional 3 h while temperature arised to 25°C. The solvent was evaporated in vacuo, water (200 ml) was added to the residue and the mixture was left with stirring overnight. The solid was filtered off, washed with water, dried in air and recrystallized from methanol. Yiellow prisms. Yield 2.78 g (74%); mp 185- $-187^{\circ}$ C.  $v_{max}$  (KBr) cm<sup>-1</sup> 3349, 3279 (NH), 1321, 1158 (SO<sub>2</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  2.63 (d, 6H, J=5.4 Hz, CH<sub>3</sub>), 4.95 (q, 2H, J=5.4 Hz, NH), 7.36-7.48 (m, 4H, ArH), 7.85 (dd, 2H, J=7.6 and 1.6 Hz, ArH), 7.95 (dd, 2H, J=7.2 and 2.1 Hz, ArH). Found: C, 33.40; H, 3.48; N, 5.73; S, 13.20. C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>Se<sub>2</sub> (499.33) requires C, 33.74; H, 3.24; N, 5.62; S, 12.87.

**2-Methylbenz-2,3-azaselenathiophene 1,1-dioxide (4a).** The mixture of diselenide **3a** (0.498 g, 0.0010 mol), benzoyl peroxide (0.266 g, 0.0011 mol) and benzene (25 ml), protected against moisture, was stirred at temperature 70°C for 24 h. Benzene was evaporated in vacuo from the mixture and the residue was chromatographed on silica gel column using dichloromethane as an eluent. The fractions containing compound **4a** were collected, and the product wasrecrystallized from carbon tetrachloride. White needles. Yield 0.262 g (54%); mp 98-100° C,  $v_{max}$  (KBr) cm<sup>-1</sup> 1327, 1172, 1159 (SO<sub>2</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  3.24 (s, 3H, CH<sub>3</sub>), 7.47 (td, 1H, J=7.4 and 1.0 Hz, ArH), 7.52 (d, 1H, J=7.5 Hz, ArH), 7.61 (td, 1H, J=7.5 and 1.1 Hz, ArH), 7.78 (d, 1H, J=7.7 Hz, ArH). Found: C, 33.68; H, 2.71; N, 5.78; S, 13.08. C<sub>7</sub>H<sub>7</sub>NO<sub>2</sub>SSe (496.31) requires C, 33.88; H, 2.84; N, 5.64; S, 12.92.

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