Organic Disulfides and Related Substances. 47. Some Novel Types of Aminoalkyl Disulfides†

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Several novel types of amino disulfides are reported, together with their stabilities in D_2O (i.e., resistance to disproportionation). These disulfides contain the group $H_2N(CH_2)_2$, known to be radioprotective, as an R group in alkenyl and arylene systems of the structure $RSSCH_2—\dot{C}=\dot{C}—CH_2SSR$. The disulfides (5–7) were synthesized by reactions of 2-aminoethanethiol with novel thiosulfonates (1–3).

Discussion

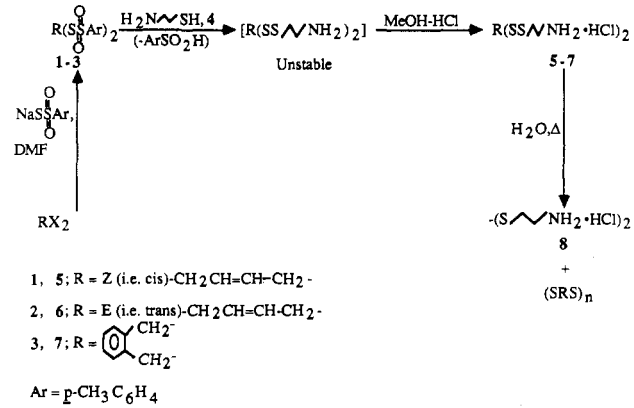
The synthesis of the bis(aminoalkyl) disulfides **5–7** (Scheme I) was initiated to examine structural types different from others we have examined previously, in relation to protection afforded by derivatives of 2-aminoethanethiol against ionizing radiation (cf., for example, ref *1*). Bis(aminoalkyl) hydrochlorides were reported earlier, but unlike the new compounds the two disulfide groups previously either were on one carbon atom, i.e., in the form of $RCH(SSR')_2$, or were attached in a 1,2-relation directly onto an aromatic ring rather than through an intervening CH_2 group (*2*).

The requisite thiosulfonates **1–3** were obtained by reaction of the corresponding halides with a 4–50% excess of sodium *p*-toluenethiosulfonate dihydrate in DMF (Scheme I). Hayashi et al. reported a melting point for **3** of 75 °C (*3*), much lower than ours (94–95.5 °C). This large difference in melting point can be attributed either to the fact that they isolated another crystalline form of **3** or that a 2-(mercaptomethylbenzyl)thiosulfonate formed which then cyclized to 1,4-dihydro-2,3-benzodithiin [mp 78–79 °C (*4*)].

The syntheses of the disulfide hydrochlorides **5–7** were achieved by the reaction of ca. 1.8 M proportions of the thiol **4**, with care to prevent oxidation, with the thiosulfonate (**1–3**) at 0 °C under Ar in the dark (to give the unstable free amino disulfides shown in brackets), followed quickly by addition of HCl(g)–MeOH because of the instability of the free base (Scheme I). The free bases of the hydrochlorides **5–7** could not be isolated.

Since information about the resistance to disproportionation of unsymmetrical disulfides to symmetrical ones is crucially important in working with them, the disproportionations of **5–7** were studied in D_2O at 68 °C (Scheme I). Several results deserve the reader's attention: (i) The (*Z*)-disulfide **5** disproportionated to give, eventually, the soluble symmetrical disulfide **8**, shown in Scheme I (as evidenced by comparison of NMR spectra with that of authentic **8**), along with the insoluble polymeric disulfide represented by $(SRS)_n$. The aryl disulfide **7** behaved similarly. It seems likely that formation of the heterocyclic 1,2-dithiins, which then polymerized, played a role with both of these disulfides. (ii) The Z-isomer **5** first isomerized to the E-isomer **6** (though this isomerization was never quite complete), which then disproportionated into **8** and the polymer (evidence was disappearance of **5**, appearance of **6**, and then disproportionation of **6**. (iii) The order of decreasing stability was **7** ≫ **6** ≫ **5**.

Scheme I



Our intention is to combine the radioprotective activities of these compounds, when available, with data from a considerable number of other compounds for publication elsewhere when all data are complete.

Experimental Section

Melting points were determined by using a Thomas-Hoover stirred-liquid apparatus and are corrected. ^1H NMR spectra are reported in parts per million (δ) and were recorded on a JEOL-FX-90Q (90 MHz) or IBM NR/300 FTNMR (300 MHz) spectrometer in D_2O. ^{13}C NMR spectra were obtained at 22.5 MHz with a JEOL-FX-90Q spectrometer. IR spectra were recorded on a Perkin-Elmer Model 727 spectrometer; the 3–4 strongest bands are indicated (*s*); others were medium or weak. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN; "Anal" signifies that elemental analyses for the elements specified were submitted for review and were within ±0.4% of calculated values (any divergencies are shown below). Extracts were dried over anhydrous $MgSO_4$, and solvent then was removed with a Buchi Rotavapor-R under reduced pressure. TLC was done using silica gel plates (Eastman Chromagram; catalog no. 13181, with fluorescent indicator) with visualization by UV or I_2 vapor. Sodium *p*-toluenethiosulfonate, $p\text{-}H_3CC_6H_4SO_2SNa$, was prepared from sodium *p*-toluenesulfinate dihydrate and sulfur following a reported method (*5*). All other chemicals not reported were commercial ones. All solvents used were predegassed by bubbling Ar through them for ca. 15 min.

(Z)-1,4-Bis(p-tolylsulfonylthio)-2-butene (1). On the basis of a reported procedure for a quite different thiosulfonate (*6*), (*Z*)-(*cis*)-1,4-dichloro-2-butene (6.25 g, 50.0 mmol) and sodium *p*-toluenethiosulfonate dihydrate (27.06 g, 110.0 mmol) were stirred in DMF (90 mL) for 60 h at 25 °C followed by 10 h at 50 °C (TLC). The mixture then was cooled, poured into H_2O (1000 mL), and extracted ($CHCl_3$). Drying and evaporation of the H_2O-washed extract gave **1** as a transparent slightly orange viscous oil; yield, 20.30 g (95%) [the crude **1** was 83% pure according to the method of Barnard and Cole (*7*)]. The analytical sample was obtained by flash chromatography of 1.50 g (yield 1.18 g, overall yield 75%) on 100 g of silica gel (column diameter 40 mm) using 10% EtOAc in hexane: R_f

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0.38 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) δ 7.74–7.30 (dd, 8 H), 5.44 (t, 2 H), 3.62 (d, 4 H), 2.46 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 144.93, 142.15, 129.85, 127.22, 126.89, 32.25, 21.40; IR (neat) 3100–2850 (br), 1670, 1590, 1485, 1400, 1320 *s*, 1300, 1180, 1140 *s*, 1080, 1015, 805 *s*, 695, 650 *s* cm^{-1}. Anal. (CH): Calcd for $C_{18}H_{20}O_4S_4$, S 29.92. Found 29.30.

Efforts to purify **1** by vacuum distillation resulted in complete polymerization.

(E)-1,4-Bis(p-tolylsulfonylthio)-2-butene (2). Essentially with the procedure used for **1**, (*E*)-(trans)-1,4-dichloro-2-butene (0.60 g, 4.8 mmol; solids in the commercial product were removed by filtration through silica gel) and sodium *p*-toluenethiosulfonate dihydrate (2.46 g, 10.0 mmol), stirred in DMF (25 mL) at 25 °C for 20 h and then at 65 °C for 2 h, yielded crude **2** in 99% yield as solid (mp 118–125 °C), which after recrystallization (MeOH) gave only 0.50 g (24%) of pure **2** as yellowish white crystalline solid (apparently because of loss by polymerization): mp 135–137 °C; R_f 0.34 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) δ 7.75–7.34 (dd, 8 H), 5.50 (m, 2 H), 3.52 (d, J = 5.6 Hz, 4 H), 2.44 (s, 6 H); IR (Nujol) 1590, 1405, 1315 *s*, 1305, 1290 *s*, 1130 *s*, 1115, 1070, 960, 810, 720, 700, 655 *s* cm^{-1}. Anal. (CHS).

1,2-Bis(p-tolylsulfonylthiomethyl)benzene (3). Essentially according to the procedure used for **1**, stirring sodium *p*-toluenethiosulfonate dihydrate (14.78 g, 60.0 mmol) and α,α'-dibromo-*o*-xylene (5.28 g, 20.0 mmol) in DMF (125 mL) at 25 °C for 18 h, followed by removal at ca. 25 °C of almost all of the DMF at 0.1 Torr overnight, led to a viscous oil that solidified in a few minutes. Recrystallization from MeOH furnished white crystals of **3** (7.18 g, 75%): mp 94–95.5 °C [lit. 75 °C (*3*)]; R_f 0.43 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) 7.70–7.29 (dd, 8 H), 7.11 (s, 4 H), 4.14 (s, 4 H), 2.43 (s, 6 H); IR (Nujol 1590, 1325 *s*, 1315 *s*, 1305, 1285, 1145 *s*, 1075, 810, 700 *s*, 650 *s* cm^{-1}. Anal. (CHS).

General Procedure for Amino Disulfides 5–7. The general procedure for the preparation of hydrochlorides **5–7** was as follows, except for variations reported in the purifications below. In a typical experiment, a solution of 2.75 mmol of thiosulfonate in $CHCl_3$ (ca. 3–4 mL/mmol) was added (1 min) to a stirred solution of 5.00 mmol of the aminothiol **4** (Aldrich Chemical Co.; pressed between sheets of filter paper to remove oil) in MeOH (ca. 3 mL/mmol) at 0 °C under Ar in the dark. After 10 min a 50% excess of 2.66 N HCl(g)–MeOH was added, followed by 30 min of stirring. After concentration to ca. $^1/_3$ volume the product was precipitated by adding $CHCl_3$ and was removed by centrifugation, washed with benzene and dried under vacuum. Variations and properties were as follows:

(a) (Z)-1,4-Bis(2-aminoethyldithio)-2-butene Dihydrochloride (5). From **1** (1.18 g, 2.75 mmol), **4** (0.386 g, 5.01 mmol), and 2.83 mL of 2.66 N methanol–HCl(g) (7.53 mmol), 0.657 g (76%) of crude **5** was obtained. A solution of **5** in MeOH (15 mL) was passed through Celite and 100 mL of $CHCl_3$ was then added. The precipitate was removed quickly (centrifugation). The solution was concentrated to 20 mL, after which Et_2O (150 mL) precipitated 0.300 g (35%) of **5**: mp 164.5–166 °C (dec); R_f 0.36 (10% MeOH in Me_2CO); ^{1}H NMR (D_2O) δ 5.68 (t, J = 5.5 Hz, 2 H), 3.42 (d, J = 6.8 Hz, 4 H), 3.23 (t, J = 5.6 Hz, 4 H), 2.86 (t, J = 6.4 Hz, 4 H); IR (Nujol) 3100–2650 (br), 1605 *s*, 1505, 1300, 1255, 1205 *s*, 1170, 1150, 1070, 1020, 940, 780 *s*, 760, 720 *s* cm^{-1}. Anal. (CHN): Calcd for $C_8H_{20}Cl_2N_2S_4$. S, 37.35. Found 37.76.

In large-scale preparation, purification was best achieved in small portions (0.5–1.0 g).

(b) (E)-1,4-Bis(2-aminoethyldithio)-2-butene Dihydrochloride (6). After reaction of 1.18 g (2.75 mmol) of **2** with **4** (0.386 g, 5.01 mmol), and 2.83 mL of 2.66 N methanolic HCl(g) (7.53 mmol), the 0.700 g (81%) of crude **6** obtained was dissolved in MeOH (15 mL). Precipitation with $CHCl_3$ (125 mL) furnished 0.190 g (22%) of pure **6** as a white solid: mp 166.5–167 °C (dec); R_f 0.36 (10% MeOH in Me_2CO); ^{1}H NMR (D_2O) δ 5.65–5.60 (m, 2 H), 3.28 (d, J = 5.3 Hz, 4 H), 3.23 (t, J = 6.4 Hz, 4 H), 2.83 (t, J = 6.4 Hz, 4 H); IR (Nujol) 3200–2600 (br), 1600 *s*, 1410 *s*, 1260, 1215 *s*, 1140 *s*, 1065 *s*, 955 *s*, 940, 925, 865, 765, 720 *s* cm^{-1}. Anal. (CNS): Calcd for $C_8H_{20}Cl_2N_2S_4$ H, 5.87. Found 5.38.

(c) 1,2-Bis(2-aminoethyldithiomethyl)benzene Dihydrochloride (7). The thiosulfonate **3** (1.316 g, 2.75 mmol), **4** (0.386 g, 5.01 mmol) and methanolic HCl(g) (7.53 mmol, i.e., 2.83 mL of 2.66 N) gave 0.543 g (55%) of analytically pure **7**: mp 213–214 °C (dec); R_f 0.42 (10% MeOH in Me_2CO); ^{1}H NMR (D_2O) δ 7.30–7.21 (m, 4 H), 4.00 (s, 4 H), 3.00 (t, J = 6.4 Hz, 4 H), 2.45 (t, J = 6.4 Hz, 4 H); IR (Nujol) 3200–2600 (br), 1600, 1570, 1510 *s*, 1490 *s*, 1405, 1325, 1250, 1230, 1125, 1100, 1080, 1050, 1040, 940, 910, 880, 800, 770 *s*, 750, 690 *s* cm^{-1}. Anal. (CHNS).

Larger preparations of **7** were contaminated with 1% or less of cystamine hydrochloride (NMR) but could be purified by redissolution in a minimum of MeOH and precipitation with $CHCl_3$.

Studies of Disproportionation by NMR. A solution of the sample (ca. 10 mg) in D_2O (ca. 0.5 mL) in a NMR tube was stoppered under Ar and then was kept at 68 °C in the dark. Disproportionation % was calculated by the relative integrals of sharp peaks corresponding to a fixed number of protons in one of the products, and the starting material. Disproportionation normally was followed until no further change was seen. For example: with **7**, cystamine dihydrochloride [**8**; δ = 3.23 (t, 2 H), 2.86 (t, 2 H)] gave a clearly distinct peak at δ 2.86 instead of at δ 2.45 for **7**. The % disproportionation was calculated as (integral for δ 2.86) (100)/(integral for δ 2.86) + (integral for δ 2.45). The identity of **8** was proved by a direct comparison with NMR spectra of authentic **8**. For **5–7**, % disproportionation (time in h), was as follows: **5**, 29 (0.2), 67 (1), 84 (4), 90 (96); **6**, 22 (6), 37 (24), 55 (72), 90 (192); **7**, 4 (8), 18 (66), 42 (203), 68 (1023). The relative rates of **5–7** (see Discussion) are more readily apparent if plots are made by using the four points shown that were selected for each.

Registry No. **1**, 111238-61-0; **2**, 111238-62-1; **3**, 1855-05-6; **4**, 60-23-1; **5**, 111238-63-2; **5**·2HCl, 111238-66-5; **6**, 111238-64-3; **6**·2HCl, 111238-67-6; **7**, 111238-65-4; **7**·2HCl, 111238-68-7; (*Z*)-$ClCH_2CH$=$CHCH_2Cl$, 1476-11-5; (*E*)-$ClCH_2CH$=$CHCH_2Cl$, 110-57-6; 2-$BrCH_2C_6H_4CH_2Br$, 91-13-4; 4-$H_3CC_6H_4SO_2SNa$, 3753-27-3.

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