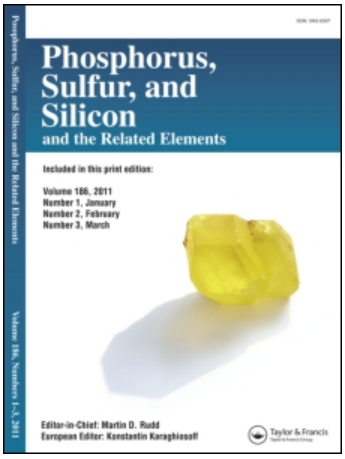

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SULFINIC ACIDS AND RELATED COMPOUNDS. 20. SYNTHESIS AND PROPERTIES OF SOME α, ω-ALKYLENEBIS(DITHIOALKANE-SULFINATES)

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SULFINIC ACIDS AND RELATED COMPOUNDS. 20. SYNTHESIS AND PROPERTIES OF SOME α,ω-ALKYLENEBIS(DITHIOALKANE-SULFINATES)[1,2]

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Title compounds (**1, 3, 4**) having the structure $NaO_2S(CH_2)_nSS(CH_2)_mSS(CH_2)_nSO_2Na$ were prepared with $m = 4$ and $n = 3$–5 by reaction of 1,4-butanedithiol with cyclic disulfide 1,1-dioxides. Products were prepared similarly where a hydrogen atom in the 2- and 3-positions of the $(CH_2)_4$ moiety was replaced with OH in *erythro* (**12**) and *threo* (**14**) relationships; careful exclusion of oxygen was necessary. The products **1, 3,** and **4** when heated in D_2O in the dark gave 1,2-dithiane (**6**) and the appropriate bissulfinate, $[NaO_2S(CH_2)_nS]_2$, apparently by a heterolytic mechanism. The relative stabilities (for $m = 4$) were $n = 5 \gg 3 > 4$. Under UV light **1, 3,** and **4** reacted more rapidly and at about the same rate as one another, apparently by a homolytic mechanism. The two dihydroxy products (**12** and **14**) were considerably less stable in solution than **1, 3,** and **4** but underwent the same type of reaction, as shown by comparison of spectra of the products with those of authentic mixtures. At ca. 25°C, the half-survival time for **12** and **14** was only ca. 25 min, and change was complete after ca. 80 min. The reaction of **14** appeared to be concentration independent and therefore may be first order.

Key words: Antiradiation Agents; Bisdisulfides; Bissulfinates; Disulfides; Disulfides dihydroxy; Sulfinic Acids.

INTRODUCTION

The α,ω-alkylenebis(dithioalkanesulfinate) **1** afforded promising protection of mice against otherwise lethal effects of ionizing radiation (e.g. 80% survival at a dose ip of 600 mg/kg; approximate LD_{50} 1000 mg/kg).[3] The analogue **2,** which consequently was synthesized,[4] also appears to be promising (50% survival of mice at a dose ip of 38 mg/kg; LD_{50} ca. 200 mg/kg).[5] Interesting differences were found in the chemistry of **1** and **2**; thus an aqueous solution of **1** became turbid within 5 min and extraction after 4 h led to isolation of the cyclization product **5** ($n = 4$) in 54% yield, but nothing could be extracted from a solution of **2** even after 24 h.[4] Further variations accordingly became both of chemical and medicinal interest. This paper reports the chemical effects of varying n and of introducing functional groups into the alkylene moiety (we anticipate that data on biological effects will be combined with data from a large number of other antiradiation agents for publication elsewhere).

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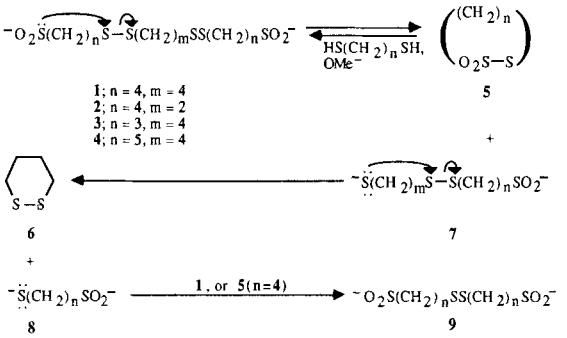


SCHEME 1

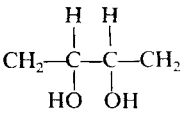
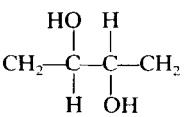
RESULTS AND DISCUSSION

The novel disulfide-disulfinates **3** and **4** were prepared essentially by the method used for **1** and **2**,[4] i.e. by reaction of 1,4-butanedithiol with the appropriate disulfide dioxide **5** ($n = 3$ and 5, respectively; Scheme 1). After a reaction period of ca. 5 min (to minimize disproportionation), the sulfinates were precipitated with Et_2O and purified by partial reprecipitation. The sulfinates **1–4** result from kinetically controlled reactions. In due course in H_2O, they undergo thermodynamically controlled equilibrations, as illustrated in Scheme 1.

In order to compare the relative stabilities of **1, 3,** and **4** in D_2O, solutions were heated at 68°C in the dark while ^1H NMR spectra were followed.[2] Table I

TABLE I

Relative stabilities of α,ω-alkylenebis-(dithioalkanesulfinates) in D_2O,[a] $NaO_2S(CH_2)_nSSXSS(CH_2)_n$-$SO_2Na$

			Change, %[b]				
			Dark			UV	
Compound no.	n	X	Temp, °C	Time, min	Change, %	Time, min	Change, %
1	4	$(CH_2)_4$	68	5	87	10	40
				10	100	60	100
3	3	$(CH_2)_4$	68	10	56	10	40
				25	100	60	100
4	5	$(CH_2)_4$	68	40	60	10	40
				220	100	60	100
12	4		ca. 25	25	50	[c]	[c]
				80	100		
14	4		ca. 25	25	50	[c]	[c]
				80	100		

[a] For values with **14** in MeOH-d_4, see the discussion.
[b] Calculated as described in the Experimental Section, up to the point where change ceased.
[c] Not studied because of the rapid reaction, even at ca. 25°C.

summarizes the results. Previously, with the tetramethylene disulfide **1** in H_2O at ca. 25°C, extraction gave 1,2-dithiane 1,1-dioxide (**5**, $n = 4$) in 66% yield after 16 h.[4] In marked contrast, NMR showed that **1** in D_2O at 68°C underwent complete change in only 10 min to give a mixture of 1,2-dithiane (**6**), which may have contained some polymeric equivalent, and the symmetrical disulfide-bissulfinate **9** ($n = 4$); the identity of these products was confirmed by congruency of appropriate parts of the NMR spectrum of the product mixture with that of a D_2O solution of authentic **9** ($n = 4$),[1b] and of a $CDCl_3$ solution of **6** (with allowance for differences of ca 0.1 ppm caused by difference in the solvents). The difference in behavior can be explained as shown in Scheme 1. At ca. 25°C, no doubt the dioxide **5** ($n = 4$) was extracted almost as soon as it was formed, before it could react further (the other product presumably was largely the water-soluble salt **7**, ($m = n = 4$). At 68°C, on the other hand, Scheme 1 illustrates how a neighboring-group effect in the initial product **7** ($m = n = 4$) could lead to cleavage into 1,2-dithiane (**6**) and the thiolate ion **8** ($n = 4$); reaction of **8** with **1** or the disulfide dioxide **5** ($n = 4$) then would produce the other product characterized, the symmetrical bissulfinate **9** ($n = 4$). NMR spectra after the 10-min period at 68°C were consistent with these conclusions.[2,6]

The tri- and pentamethylene counterparts followed the same course of reaction, also becoming turbid soon after being heated. Despite the presence of the (finely divided) solid phase, however, changes in the NMR spectra could be followed readily (although the peaks for the dithiane, **6**, were broadened). With the trimethylene compound **3**, NMR indicated that complete conversion occurred in 25 min at 68°C to 1,2-dithiane (**6**) and the symmetrical disulfide **9** ($n = 3$).[2,7] The nature of the products from the tri- and pentamethylene counterparts (**3**, **4**) followed from the same kinds of evidence used for the tetramethylene compound (**1**). The pentamethylene sulfinate (**4**) was considerably more stable than the tetra or trimethylene counterparts (**1** and **3**, respectively). NMR spectra indicated complete change only after 220 min.[2,8] With none of the three compounds (**1**, **3**, **5**) was there any indication after the reaction was complete of the presence of 1,2-dithiane 1,1-dioxide (**5**, $n = 4$), which had been isolated previously at lower temperatures (no resonance at ca. δ 3.3–3.4 for $-CH_2SO_2S-$).[9]

The three disulfides (**1**, **3**, and **4**) proved sufficiently sensitive to UV light to indicate that unnecessary exposure to ambient light should be avoided. It is interesting that under UV light all three disulfides were about equally stable, as one would expect if they were reacting homolytically. Table I summarizes the results. These results are in marked contrast to the reactions of Scheme 1, where the slow reaction of the pentamethylene disulfide (**4**), compared with **1** and **3**, indicates that thermally-induced reactions in the dark are heterolytic. We have observed previously that reactions of disulfides can be either predominantly homolytic under UV or heterolytic when heated in the dark (cf., for example, ref. 10). The reactions under UV light gave complex NMR spectra (indicating more complex reactions than those thermally induced), although NMR indicated that 1,2-dithiane (**6**) and the symmetrical bissulfinate **9** were among the products. Nevertheless, the % of change as a function of time could be estimated reasonably well.

The dihydroxypropyl disulfide **10** had promising radioprotective activity (90–100% survival of mice at ip doses of 150–600 mg/kg; LD_{50} ca. 1000 mg/kg).[5] In

view of the promise

$$HOCH_2CH(OH)CH_2SS(CH_2)_4SO_2Na$$

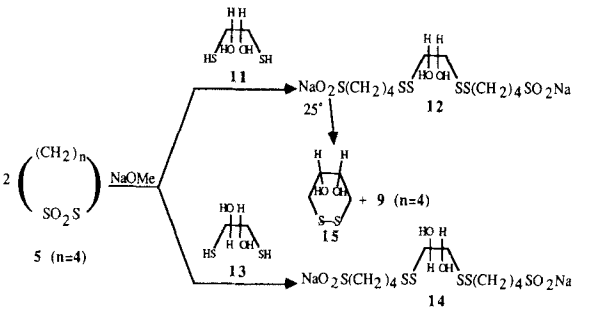
10

mentioned of **1**, an attractive possibility was combination of the bisdisulfide feature of **1** with the dihydroxyalkyl feature of **10** in structures **12** and **14** (Scheme 2). Chemically, **12** and **14** were desired for assessment of the effects of substituents on the stability of compounds of structure **1** in solution.

Preparation of the erythro salt **12** first was attempted without special precautions, in the manner used for **1–4**, i.e. by addition of methoxide ion to a mixture of the dithiol **11** and dioxide **5** (Scheme 2). However, **11** (like **13**) is a well-known reducing agent and was oxidized readily (presumably to **15**). Hence, because of the lack of **11**, the dithiane dioxide (**5**, $n = 4$) reacted with NaOMe to give the bissulfinate **9** ($n = 4$), a known reaction.[11] Careful purging of the solvent with argon and operation under argon circumvented the oxidation of **11**. Even so, a second problem arose when freeze-drying of the aqueous solution of **12** led to significant oxidation of sulfinate to sulfonate groups (NMR, IR).[2] Ultimately, a short reaction time (1-2 min) under argon, followed by precipitation with ether from the MeOH used as solvent gave **12** in 84% yield. Essentially the same procedure with dithiothreitol (**13**) gave **14** in 85% yield.

Both **12** and **14** reacted astonishingly rapidly in D_2O. Both had a half-survival time of only ca. 25 min at ca. 25°C, and both had totally changed within 80 min (Table I). That the products from the erythro salt **12** were the expected **9** ($n = 4$) and **15** was confirmed after the 80-min period by congruency of a NMR spectrum of the solution with one of a 1:1 mixture of **9** ($n = 4$) and **15**. The reaction of the *threo* salt **14** appears to be first-order, since reactions seemed concentration independent; thus at concentrations of 5 and 50 mM in MeOH-d_4 each was complete in ca. 260–300 min, with a half-survival time of ca. 80-135 min; we have observed first-order reactions previously with disulfides more amenable to kinetic study.[10,12] Comparison with Table I indicates that the reaction is about four-fold faster in H_2O than in MeOH; we have commented before on rate enhancements of this kind.[12c] The disulfides **12** and **14** were stable as solids when kept dry at ambient conditions, at least for several weeks.

We described previously the effect of another variable, in the central alkylene portion of bis(dithioalkanesulfinates), viz. chain length;[13] thus when n was kept at



SCHEME 2

4 as in **1** and **2**, but m was 3 or 5, the products in H_2O at ca. 25°C were polymer and **5** ($n = 4$) as the only other material isolated.[13]

EXPERIMENTAL

All ^{13}C NMR spectra were determined using a JEOL-FX-90Q spectrometer at 22.5 MHz. Otherwise the details of instrumentation, starting materials, and procedures were as described previously;[1b] as before, data included for spectra have not been reported heretofore.

Disodium 1,4-Tetramethylenebis (3'-dithiopropanesulfinate) (**3**). Essentially according to the procedure reported for **1**,[4] a solution of Na (0.500 g, 21.7 mg atom) in MeOH (20 mL) was added dropwise (15 min) to a solution of 1,2-dithiolane 1,1-dioxide (**5**, $n = 3$; 3.00 g, 21.7 mmol)[1b] and 1,4-butanedithiol (1.33 g, 10.9 mmol) in MeOH (35 mL) at ca. 20°C. After a stirring period of 5 min, the salt **3** was precipitated by addition of Et_2O (400 mL). The precipitate was dissolved in MeOH (50 mL), ca. 10% was precipitated with Et_2O (35 mL) and discarded, and the remaining **3** was precipitated with 300 mL of Et_2O; yield of **3** as white solid, 3.95 g (82%): ^1H NMR (90 MHz; D_2O, DSS) δ 2.60–3.00 (m, 8), 2.28–2.56 (t, 4), 2.16–1.60 (m, 8); ^{13}C NMR (D_2O, DSS) δ 63.89, 41.96 (2 peaks), 31.40, 25.62; IR (Nujol) 1400, 1295, 1000 (broad, s), 720 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}Na_2O_4S_6$: C, 27.15; H, 4.52; S, 43.44. Found: C, 27.08; H, 4.44; S, 43.42.

Disodium 1,4-Tetramethylenebis(4'-dithiobutanesulfinate) (**1**) was prepared as described for **3** (70% yield); it had appropriate ^1H NMR spectra.[4]

Disodium 1,4-Tetramethylenebis (5'-dithiopentanesulfinate) (**4**). The procedure for **3** gave **4** in a yield of 2.58 g (81%) from Na (0.293 g, 12.76 mg atom), 1,4-butanedithiol (0.80 g, 6.54 mmol), and 1,2-dithiepane 1,1-dioxide (**5**, $n = 5$; 2.22 g, 13.4 mmol):[1b] ^1H NMR (CD_3OD, 90 MHz) δ 2.52–2.80 (m, 8), 2.12–2.36 (m, 4), 1.28–1.88 (m, 16); ^{13}C NMR (CD_3OD) δ 63.03, 39.68, 39.36, 30.09, 29.17, 28.90, 23.21; IR (Nujol) 1420, 1000 (broad, s), 920, 730 cm^{-1}.

Anal. Calcd for $C_{14}H_{28}Na_2O_4S_6$: C, 33.72; H, 5.62; S, 38.54. Found: C, 33.73; H, 5.39; S, 38.42.

Disodium erythro-2,3-dihydroxy-1,4-tetramethylenebis(4'-dithiobutanesulfinate) (**12**). Methanol used was purged to remove O_2 by passage of Ar for ca. 10 min, and the reaction was carried out under Ar, with precautions at all points for exclusion of O_2. A solution of Na (0.446 g, 19.4 mg atom) in MeOH (10 mL) was added with good stirring (2 min) to a solution of the dioxide **5** ($n = 4$) (3.70 g, 24.3 mmol) and dithioerythritol (**11**; 1.50 g, 9.72 mmol) in MeOH (20 mL) at 10-15°C. After a stirring period of 2 min, the salt **12** was precipitated with Me_2CO(300 mL). The **12** was redissolved in MeOH (20 mL), ca. 5% was precipitated with Et_2O (15 mL) and removed by centrifugation, and the rest of the **12** then was precipitated by Et_2O (300 mL); yield of **12**, 4.10 g (84%): IR (Nujol) 3600-3100, 1040, 1000 (br, s), 720 cm^{-1}; ^1H NMR (CD_3OD; 300 MHz) δ 3.70-3.78 (m, 2H), 3.10 (dd, 2H), 2.68-2.80 (m, 6H), 2.27 (t, 4H), 1.64-1.86 (m, 8H); ^{13}C NMR (CD_3OD) δ 73.70, 62.71, 43.91, 39.36, 29.77, and 22.51.

Anal. Calcd for $C_{12}H_{24}Na_2O_6S_6$: C, 28.67; H, 4.78; S, 38.23. Found: C, 28.82; H, 4.85; S, 38.32.

Disodium threo-2,3-dihydroxy-1,4-tetramethylenebis(4'-dithiobutanesulfinate) (**14**). With the same precautions used for **12** a solution of Na (0.224 g, 9.74 mmol) in MeOH (5 mL) was added (2 min) to a solution of dithiothreitol (**13**; 0.75 g, 4.86 mmol) and the dioxide **5** ($n = 4$) (1.85 g, 12.2 mmol) in 5 mL of MeOH at 15°C. After 1 min, the **14** was precipitated with Et_2O (30 mL); yield of **14** as a hygroscopic solid, 1.62 g (66%); since the **14** was hard to handle (sticky, clumping), an effort to reprecipitate it for purification seemed unwise: IR (Nujol) 3600-3100, 1220, 1170, 1080, 950-1000 (s), 720 cm^{-1}; ^1H NMR (CD_3OD; 300 MHz) δ 3.92-4.00 (m, 2H), 3.00-2.72 (m, 8H), 2.28 (t, 4H), 1.64-1.86 (m, 8H); ^{13}C NMR (CD_3OD) δ 71.32, 62.71, 43.42, 39.57, 29.77, 22.51.

Anal. Calcd for $C_{12}H_{24}Na_2O_6S_6$: C, 28.67; H, 4.78; S, 38.23. Found: C, 28.26; H, 5.00; S, 38.65.

A second preparation on a larger scale gave **13** in 85% yield.

Studies of Stability. Solutions of 0.5 mL of the disulfide sulfinates (**1**, **3**, **4**, **12**, and **14**) at 0.05 M concentration in D_2O were kept in the dark at room temperature (ca. 25°C) or were heated at 68°C, as stated (Table I), in the 300-MHz NMR probe, while ^1H NMR spectra were taken at the intervals reported. DSS was used as the internal standard. Disproportionations under UV light were done by irradiating comparable solutions in NMR tubes with a 100-w Hanovia UV lamp ca. 10 cm distant; the temperature rose somewhat but never above 40°C (briefly).

For the results as to thermal stability (Table I), "change, %" was calculated as follows, where A is the integral of the peak specified as to ppm in parentheses (range indicated by the arrow), T_0 is the initial time, T is the time reported in Table I, and T_c is the time at which reaction was complete: For **1** and **4**, % = [A (2.86→2.92) at T/A (2.86→2.92) at T_c] (100); based on the increase in the peak for —SS**CH**$_2$(CH$_2$)$_2$**CH**$_2$SS of **6**). For **3**, % = [A (1.98) at T–A (1.98) at T_0] (100)/[A (1.98) at T_0]; based on the addition of the 4-H peak for —SSCH$_2$(**CH**$_2$)$_2$CH$_2$SS— to an existing quintet for —**CH**$_2$CH$_2$SO$_2$—, with the initial quintet providing a 4-H reference. For the *threo* salt **14,** since the methine peak at δ 3.96→4.04 did not totally change to one at 3.56→3.66, "change, %" = [A (3.56→3.66) at T] (100)/[A(3.56→3.66) at T_c + A (3.96→4.04) at T_c]. With the *erythro* salt **12**, a more complex calculation was based on a decrease in the 6H signal to 4H at δ 2.68→2.80, referred to a constant 4H signal at δ 2.34.[2]

In the experiments with UV light, for the 10-min time of **1** and **4**, "change, %" = [A (2.85→2.95) at T] (100)/[A (2.37) at T, as a 4-H reference] (based on the formation of —SS**CH**$_2$(CH$_2$)$_2$**CH**$_2$SS— (2.85→2.95), with unchanging —**CH**$_2$SO$_2$— (2.37) as a standard; "100% change" was based on cessation of change for **CH**$_2$SS of **9** (n = 4,5) at 2.75→2.80. For **3**, "change, %", was based on a decrease in the 4-H peak at 1.78→1.84 (—SSCH$_2$(**CH**$_2$)$_2$CH$_2$SS—) related to the constant 4-H peak at δ 2.42 (—**CH**$_2$SO$_2$—).

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6. Thus the peak of **1** at δ 1.62–1.73 for —**CH**$_2$CH$_2$SO$_2$— (m, 4H) was essentially unchanged in the salt **9** (n = 4). Half of the four peaks in **1** for —SSCH$_2$**CH**$_2$— (δ 1.76–1.88; m, 8H) remained for the salt **9** (n = 4) and half led to a new peak for 1,2-dithiane (**6**; 1.94–2.06, very broad singlet, the breadth attributable to **6** in suspension). The 2 × 2-H triplet for —**CH**$_2$SO$_2$— at δ 2.36–2.43 did not change significantly, while a multiplet for 4 × —**CH**$_2$SS— (8H, δ 2.74–2.86) separated into a peak for 1,2-dithiane at δ 2.84–2.92 (again a very broad singlet with fine structure; 4-H) and another at δ 2.77–2.82 for 2 × —**CH**$_2$SS of the salt **9** (n = 4).
7. The signal for —SSCH$_2$(**CH**$_2$)$_2$CH$_2$SS— of **3** at δ 1.78–1.84 (4H, m) virtually disappeared and a new signal appeared for it in the dithiane **6** (δ 1.98, m, 4H) under an existing 4H quintet for —O$_2$SCH$_2$**CH**$_2$CH$_2$S. The triplet for —O$_2$S**CH**$_2$— did not change significantly (4H, 2.42–2.48). Meanwhile, the signal for —SS**CH**$_2$(CH$_2$)$_2$**CH**$_2$SS— at δ 2.80 (t, 4H) changed to that for 1,2-dithiane (**6**) under the existing triplet for —O$_2$SCH$_2$CH$_2$**CH**$_2$S at δ 2.84 (t, 4H). The final mixture thus showed the following resonances: δ 1.91–2.06 (appearance of a quintet, 8H) for —O$_2$SCH$_2$**CH**$_2$CH$_2$S and —SSCH$_2$(**CH**$_2$)$_2$CH$_2$SS—; 2.39–2.44 (t, 4H) for 2 × **CH**$_2$SO$_2$—; 2.78–2.94 (appearance of a triplet, 8H) for —SS**CH**$_2$(CH$_2$)$_2$**CH**$_2$SS, plus 2 × $^-$O$_2$S(CH$_2$)$_2$**CH**$_2$SS.
8. The initial spectrum of **4** was much like that of **1**, except for resonances for 8H at δ 1.42–1.68 for —SS(CH$_2$)$_2$(**CH**$_2$)$_2$CH$_2$SO$_2$Na rather than for 4H at 1.74–1.62 for —SS(CH$_2$)$_2$**CH**$_2$CH$_2$SO$_2$Na of **1**. The dithiane **6** and bissulfinate (**9**, n = 5) were formed as usual, but part of the dithiane appeared to have reacted further.
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