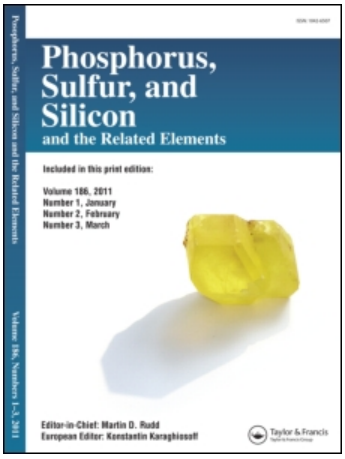

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SULFINIC ACIDS AND RELATED COMPOUNDS. 16. SYNTHESES AND PROPERTIES OF SOME 4-(ALKYLDITHIO)- AND SUBSTITUTED 4-(ALKYLDITHIO)BUTANESULFINATE SALTS[1]

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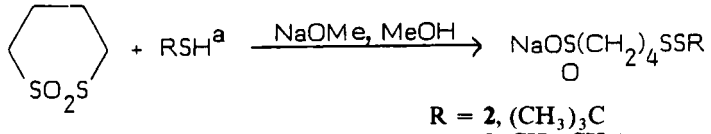
Alkyl- and substituted alkyldithiobutanesulfinate salts of the structure $RSS(CH_2)_4SO_2Na$ were prepared in 62–81% yield by cleavage of 1,2-dithiane 1,1-dioxide (**1**) by thiolate salts. Compounds are reported with R = $(CH_3)_3C$ (**2**), $CH_3(CH_2)_3$ (**3**), CH_3CH_2 (**4**), $HO(CH_2)_2$ (**5**), $HO_2CCH_2CH(CO_2H)$ (**6**), $NaO_2S(CH_2)_4SS(CH_2)_3$ (**7**), and $NaO_2S(CH_2)_4SS(CH_2)_5$ (**8**). These compounds disproportionated in water to permit extraction of the symmetrical disulfide RSSR (**3**, **5**), or a mixture of RSSR and the dioxide **1** (**2**, **4**), or **1** only (**6**), or **1** plus insoluble polymer (**7**, **8**). The order of increasing resistance to disproportionation, where polymer was not involved, was estimated to be **3** < **6** ~ **4** ≤ **5** ≪ **2**.

INTRODUCTION

Among a variety of disulfide-sulfinate salts and related compounds resembling those shown in Scheme 1, several have shown promise in mammalian protection against ionizing radiation.[1-7] A particularly notable feature is that some of the most promising atypically contained no nitrogen.[7] We have reported the beginning of efforts to clarify the chemistry of this class of disulfide sulfinates and at the same time to determine the types of R groups that will maximize radioprotection.[1,7,8] The present paper extends this study to the types of groups shown in Scheme 1, viz. where R is a small lipophilic or hydrophilic group or is itself a disulfide sulfinate.



1

R = **2**, $(CH_3)_3C$
3, $CH_3(CH_2)_3$
4, CH_3CH_2
5, $HO(CH_2)_2$
6, $HO_2CCH_2CH(CO_2H)$
7, $NaO_2S(CH_2)_4SS(CH_2)_n$; $n = 3$
8, **7** with $n = 5$

[a] For **7**, R of RSH = $HS(CH_2)_3$. For **8**, R of RSH = $HS(CH_2)_5$.

SCHEME 1

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RESULTS AND DISCUSSION

The preparations and purifications of **2–8** were based on earlier procedures (cf. for example refs. 7 and 8), the dioxide **1** frequently being used in excess in the preparations since it is easily removed in the purifications during precipitation of the salts (which should be completed without delay to minimize disproportionation). Table I summarizes the results. That the products in fact were **2–8** and not mixtures of symmetrical disulfides was shown by single spots in TLC and by consistency of spectra (Table I), as well as by the fact that the disproportionations to symmetrical disulfides were subsequently studied as described below.

The resistance to change of the present products in aqueous solution was of much interest, as it has been in related instances.[2-8] It was approximated by periodic extraction of the aqueous solutions. The unsymmetrical disulfides **2–5** led either to

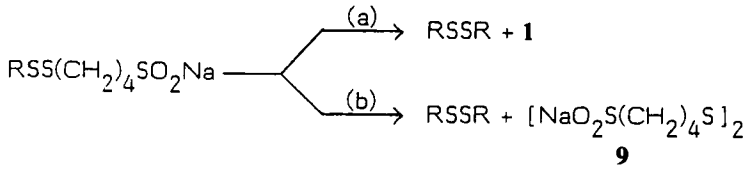
TABLE I

Preparation and properties of disulfide-sulfinate salts, $RSS(CH_2)_4SO_2Na$ (**2–8**)[a]

Compound no.	R of $RSS(CH_2)_4SO_2Na$	Reaction time, min	Yield, % (wt. loss when dried, %)[b]	R_f value[c]	IR(KBr), cm^{-1}	^1H NMR (D_2O), δ in ppm
2	$(CH_3)_3C$[d]	20	62 (1.40)	0.65	3600–3050, 2950(s), 1620, 1450, 1360, 1280, 1220, 1160, 1020(s), 1000(s), 960(s), 810, 730	3.00–2.64(t, 2 H), 2.48–2.16(t, 2 H), 1.96–1.48(m, 4 H), 1.36(s, 9 H)
3	$CH_3(CH_2)_3$	15	68 (2.91)	0.48	3550–3150, 2900, 2850, 1650, 1440, 1400, 1360, 1240, 1000(s), 980(s), 710	3.00–2.48(t, 4 H), 2.48–2.04(t, 2 H), 2.04–1.04(m, 8 H), 1.00–0.68(t, 3 H),
4	CH_3CH_2	1.5	78 (0.27)	0.56	3600–3050, 2900, 2825, 1610, 1420, 1350, 1240, 1200, 980(s), 960(s)	3.00–2.48(m, 4 H), 2.48–2.20(t, 2 H), 1.98–1.42(m, 4 H), 1.40–1.04(t, 3 H),
5	$HO(CH_2)_2$	2.0	81 (1.00)	0.53	3600–3050, 2950, 2850, 1440, 1400, 1350, 1260, 980(s), 720	3.96–3.76(t, 2 H), 3.00–2.64(m, 4 H), 2.52–2.20(t, 2 H), 2.00–1.44(m, 4 H)
6	$HO_2CCH \cdot H_2O$[e] HO_2CCH_2	1.5	79 (see footnote e)	0.26	3650–3300, 2950, 1700(s), 1600(s), 1400(s), 1310, 1000(s)	3.84–3.68(t, 1 H), 3.04–2.72(m, 4 H), 2.56–2.28(t, 2 H), 1.96–1.48(m, 4 H)
7	$NaO_2S(CH_2)_4SS(CH_2)_3 \cdot 1.25\ H_2O$[f]	5.0	64 (see footnote f)	0.66	3650–3300, 2900, 2850, 1610, 1400, 1220, 1030(s), 1010(s), 980(s), 700	3.40–2.68(q, 8 H), 2.52–2.28(t, 4 H), 2.00–1.42(m, 10 H)
8	$NaO_2S(CH_2)_4SS(CH_2)_5$	8.0	69 (4.88)	0.53	3650–3500, 2900, 2850, 1440, 1400, 1280, 1220, 1020(s), 980(s), 960(s), 720	3.00–2.64(t, 8 H), 2.52–2.20(t, 4 H), 2.00–1.44(m, 14 H)

[a] Satisfactory elemental analyses (±0.4%) were submitted for C, H, and S, except as noted by structures.
[b] Loss of weight when sample was dried to constant weight by the analyst at 110°C and atm. pressure.
[c] TLC with 15% MeOH in Me_2CO; single spots were seen in all instances.
[d] S% calcd. 36.38; found 35.91.
[e] Isolated as $6 \cdot 3H_2O$. Calcd. wt. loss for $6 \cdot 3H_2O$ to $6 \cdot H_2O$, 9.51%; found 9.49%. Calcd. for $6 \cdot H_2O$: H, 4.41%; found 3.97%.
[f] Isolated as $7 \cdot 1.75H_2O$. Calcd. wt. loss for $7 \cdot 1.75H_2O$ to $7 \cdot 1.25H_2O$, 1.87%; found 2.00%. Calcd. for $7 \cdot 1.25H_2O$: C, 27.53%; H, 5.14%. Found: C, 28.01%; H, 4.70%.

the results of eq. 1a or to those of eq. 1b; **6** gave only the dioxide **1**, while **7** and **8** gave **1** and polymer. Table II shows the results obtained with **2–8**.



(1)

The *tert*-butyl disulfide **2** and the ethyl disulfide **4** behaved according to eq. 1a. Both products (RSSR and **1**), being insoluble in water, were isolated as a mixture (TLC); the NMR spectra of the products were consistent with a mixture of RSSR and **1** formed in similar amounts (with two earlier compounds,[8] **1** alone was extracted, perhaps because of greater solubility (RSSR) or stability (RSNa) of the other product in water).

The disulfides **3** and **5** disproportionated according to eq. 1b. The symmetrical disulfide RSSR was extracted (pure) and was characterized by NMR. With **3** as an example, the other symmetrical disulfide (**9**) was isolated by evaporating the water layer and was characterized by NMR.

With the remaining disulfides (**6–8**), only the dioxide **1** was extracted, perhaps because other products were water soluble (**6**) or polymeric (**7, 8**).

In increasing resistance to disproportionation, the order was estimated to be as follows: **3** < **6** ~ **4** ≤ **5** ≪ **2** (the disulfides **7** and **8** are not included because of the

TABLE II

Disproportionation (%) of $RSS(CH_2)_4SO_2Na$(H_2O, ca. 25°C) as approximated by cumulative conversion to products[a]

Compound no.	R of $RSS(CH_2)_4SO_2Na$	Disproportionation (%) in time shown[a]				
		4 h	8 h	24 h	48 h	1 week
2[b]	$(CH_3)_3C$	1	1	1	1	2
3[c]	$CH_3(CH_2)_3$	7	11	20	36	79
4[b]	CH_3CH_2	13	20	25	31	39
5[c]	$HO(CH_2)_2$	4	8	10	14	36
6[d]	HO_2CCH HO_2CCH_2	18	19	24	27	36
7[d,e]	$NaO_2S(CH_2)_4SS(CH_2)_3$	7	9	9	12	15
8[d,e]	$NaO_2S(CH_2)_4SS(CH_2)_5$	14	16	18	20	28

[a] Where only RSSR was extracted from the aqueous solution (**3, 5**), "disproportionation, %" was calcd as (2 × mmol of RSSR extracted)(100)/(10 mmol used of unsymmetrical disulfide). Where both RSSR and **1** were extracted, the assumption was made from NMR of equal weights; the weight isolated therefore was divided by 2 and then by the mol. wt. of RSSR to get mmol of RSSR; the % probably is somewhat high, since somewhat more **1** was present (which would reduce the % calcd for disproportionation).

[b] Both RSSR and **1** were isolated. See footnote a for calculation of disproportionation, %

[c] Only RSSR was isolated (with **9** found in the aqueous layer from **3**).

[d] Only the dioxide **1** was isolated. The % disproportionation was calcd as (mmol of **1** extracted)(100)/(10 mmol used).

[e] A considerable amount of polymer also was formed (insoluble in both the H_2O and $CHCl_3$ layers).

uncertain implications of polymer). The markedly greater resistance of the *tert*-butyl disulfide (**2**) seems best attributed to a resistance conferred by the *tert*-butyl group to attack of thiolate ions on the disulfide bond. This improvement in resistance to change in aqueous solution should afford important information for the design of more stable disulfide-sulfinate salts as antiradiation agents, although the effect of improved resistance on radioprotective capability remains to be determined (our expectation is that when radioprotective data become available, the data for **2–8** will be grouped with data for related compounds studied and to be studied and published elsewhere).

EXPERIMENTAL

The ^1H NMR spectra, reported in parts per million (δ), were obtained in D_2O with a JEOL Model JNM-MH-100 spectrometer using $Me_3Si(CH_2)_3SO_3Na$ (DSS) as an internal standard (Table I). IR spectra were obtained using KBr pellets with a Perkin-Elmer Model 727 spectrometer; strong peaks are so indicated—others were medium or weak intensity (Table I). Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.; these were satisfactory for C, H, and S ($\pm 0.4\%$), except for minor divergencies noted in the footnotes to Table I. TLC was performed on Eastman Chromagram silica-gel plates (cat. no. 13181), with visualization by UV or I_2 vapor (Table I). 1,2-Dithiane 1,1-dioxide (**1**) was prepared from 1,2-dithiane using KIO_4:[9] mp 54–55°C; lit. mp 54.5–55°C.[9] All thiols used were commercial products.

Preparation of Disulfide-sulfinate Salts (**2–8**). As an example of the general method, preparation of *sodium 4-(tert-butyldithio)butanesulfinate* (**2**) was achieved by adding 0.90 g (10.0 mmol) of 2-methyl-2-propanethiol to a solution of 0.23 g (10.0 mmol) of Na in 15 mL of MeOH. The resulting solution was added dropwise with stirring during 1 min to a solution of 1.67 g (11.0 mmol) of 1,2-dithiane 1,1-dioxide (**1**) in 25 mL of MeOH at 0–5°C. Since **1** was used in excess (because it could be easily removed in the purification of **2**), completion of reaction was determined by appearance of a (strong) new spot in TLC rather than by the loss of a spot for **1**. When reaction was complete (cf. Table I; 20 min for **2**), 400 mL of dry Et_2O was added (in the subsequent centrifugations involving Et_2O, care should be taken that vapors cannot be ignited by sparking of the motor; we used an explosion-proof centrifuge). The precipitate of **2** which immediately appeared was removed by centrifugation and decantation and was dissolved in a minimum of MeOH (30 mL). For purification, enough Et_2O (35 mL) then was added to precipitate an estimated 10% of solid. The supernatant solution was separated by centrifugation and decantation and then was diluted with enough Et_2O (400 mL) to effect complete precipitation. The precipitate of **2** then was separated by centrifugation and decantation and was dried at room temperature for 24 h. Although problems frequently have been encountered with variable hydration of disulfide-sulfinate salts (cf. ref. 8, for example), **2–5** and **8** lost only small amounts of weight when redried by the analyst (Table I) and (uncharacteristically) gave satisfactory analyses for the anhydrous salts. The same method of preparation and purification was used for *sodium 4-(n-butyldithio)* (**3**), *4-ethyldithio)* (**4**) and *4-(2-hydroxyethyldithio)butanesulfinate* (**5**). For *sodium 4-(1,2-dicarboxyethyldithio)butanesulfinate* (**6**), 10.0 mmol of Na in 15 mL of MeOH was added to a solution of 11.0 mmol of **1** and 10.0 mmol of mercaptosuccinic acid in 30 mL of MeOH (the usual procedure led to a gel when the thiol was added to the methanolic alkoxide). For *disodium (1,3-propylenedithio)* (**7**) and *(1,5-pentylenedithio)bis(4-butanesulfinate)* (**8**), 5.0 mmol of 1,3-propanedithiol or 1,5-pentanedithiol was added to 10.0 mmol of Na in 15 mL of MeOH, and the solution obtained then was added to 11.0 mmol of **1** in MeOH (25 mL). Further details for **2–8** are given in Table I.

Studies of Disproportionation. The disulfide-sulfinate salts **2–8** (10.0 mmol) were dissolved in 50 mL of H_2O, and the solutions were stirred under the ambient conditions of practical interest (ca. 25°C). At regular intervals (Table II), each solution was extracted with 4–5 20-mL portions of $CHCl_3$. The extracts were dried ($MgSO_4$) and, after removal of the drying agent, were evaporated to dryness, kept at 0.5 torr overnight, and weighed. The cumulative "Disproportionation (%)" for **2–8** is shown in Table II.

Compounds **2** and **4** gave the dithiane dioxide **1**, together with di-*tert*-butyl or diethyl disulfide respectively, as shown by NMR and by TLC comparison with the three authentic materials. Since NMR spectra seemed consistent with roughly similar amounts of **1** and the disulfide in the mixture, "Disproportionation, %" for **2** and **4** was estimated as stated in Table II, footnote a.

With the disulfides **3** and **5**, extraction gave only di-*n*-butyl and di-2-hydroxyethyl disulfide respectively, both of which had appropriate NMR spectra; the identity of the butyl disulfide from **3** was

confirmed, as an example, by IR and by TLC comparison with known material. Evaporation of the aqueous layer from **3**, also as an example, gave disodium 4,4′-dithiobis(butanesulfinate) (**9**), which was precipitated from MeOH with Me_2CO in 92% yield and then had a ^{14}C NMR spectrum identical with that of authentic **9**.[10]

With **6–8**, the dioxide (**1**) extracted was identified by TLC and by identity of NMR spectra.

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