# Sulfinic Acids and Related Compounds. 12. Conversions of 1,2-Dithiane 1,1-Dioxide to 4-Mercaptobutanesulfinates and 4,4′-Polythiobis(butanesulfinates)[1,2]

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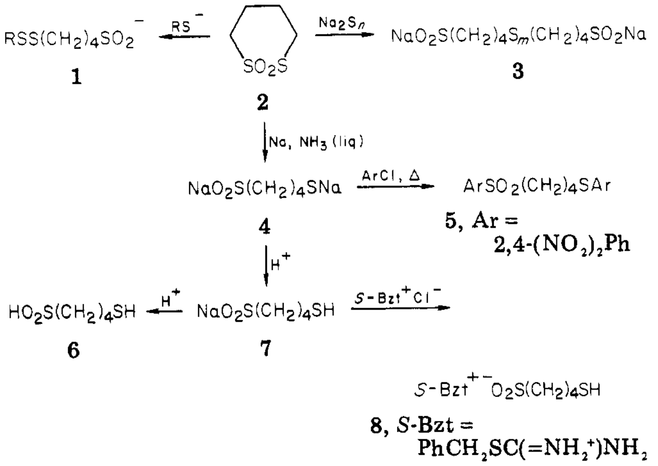
1,2-Dithiane 1,1-dioxide (**2**) was reduced by sodium in liquid ammonia to the disodium salt of 4-mercaptobutanesulfinic acid (**4**), a member of a new class, which was characterized by conversion to the sulfone–sulfide **5** with 2,4-dinitrochlorobenzene (60% yield from **2**); reduction with $NaBH_4$ led to a polymer. The mercaptosulfinic acid from **4** was an oil, but the monosodium (sulfinate) salt (**7**) gave a crystalline *S*-benzylthiouronium mercaptosulfinate (**8**, 70% yield) and also could be isolated as such in practicable purity. Sodium polysulfides, $Na_2S_n$, cleaved the dioxide **2** to give 4,4′-polythiobis(butanesulfinates), $NaO_2S(CH_2)_4S_m(CH_2)_4SO_2Na$ (**3**). When $n$ exceeded 4, sulfur precipitated during the reaction itself, and the product had $m = 5.1$–$5.5$. When $n$ was 4, $m$ was 4.9–5.8 (the highest found). When $m$ exceeded 4, however, sulfur slowly precipitated from aqueous solutions of the disulfinates and left the tetrasulfide ($m = 4$) in solution. The tetrasulfide appears to represent the maximum chain length stable for more than a few hours in water.

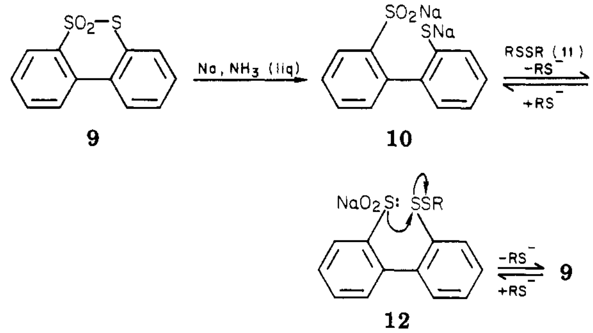
1,2-Dithiane 1,1-dioxide (**2**, Scheme I) has been used as a model for cyclic disulfide 1,1-dioxides in a general sense to demonstrate the promise of such dioxides as tools for synthesizing a variety of disulfides with both groups functionalized. For example, thiols convert the dioxide **2** to disulfide–sulfinates **1**;[1f–i] the sulfinate function then can be converted to $SO_3Na$, $SO_2R$, or $SO_2SR$.[1f] Sodium sulfide converts **2** to a trisulfide–disulfinate **3** ($m = 3$).[1h] Counterpart aromatic disulfide 1,1-dioxides undergo similar useful reactions.[1j–k] Oxidation of the 1,1-dioxide to the 1,1,2,2-tetraoxide opens up still another set of possibilities.[1f] This paper reports extension of this work with the dioxide **2** as a model. We describe reduction of the dioxide **2** to the representative potentially useful mercaptosulfinate synthon **4**, along with a study of the extent to which the polysulfide chain of **3** can be extended.

For the reduction of **2** to **4**, sodium hydride was unpromising, and sodium borohydride gave an intractable polymer. However, sodium in liquid ammonia reduced **2** to **4**. The **4** produced had strong IR bands at 1020 and 970 $cm^{-1}$, consistent with our previous experience of one strong band for $RSO_2Na$ at 1060–1000 $cm^{-1}$ and another at 1015–950 $cm^{-1}$;[1d,f–h,j,k] for $RSO_2H$ (as solids), a band at 1090–990 $cm^{-1}$ has been assigned to S=O stretch and one at 870–810 $cm^{-1}$ to S–O stretch.[3] Analysis for the thiol content of **4** by the Ellman technique showed at least 67% of the expected 1 molar equiv;[4,5] this technique may be subject to considerable variation in results, however (see Experimental Section), and we suspect that the nature of **4** introduces other complications as well that minimize the values of SH content. The identity of the disodium salt **4** was confirmed by conversion to the analytically pure sulfone–sulfide **5** in 61% yield (60% from **2**).

**Scheme I**



The generality of the reduction is suggested by the conversion of **9** to **10** in 98% yield. Interestingly, analysis with Ellman's reagent (**11**) of **10** showed 1.3 equiv of thiol rather than 1.0 equiv. As eq 1 indicates, presumably the excess of thiol over 1.0 equiv arises from facile equilibration of the initial product (**12**) with the starting material (**9**) and the (colored) Ellman thiolate fragment, $RS^-$. This contrast to the normal 1:1 equivalence of thiols with the Ellman reagent (**11**) is attributable to the very facile cyclization of **12**, a characteristic noted earlier for alkyldithioarenesulfinates.[1j,k]



(1)

$R = 3\text{-}CO_2H\text{-}4\text{-}NO_2Ph$-[1i]

Acidification of an ethanol solution of the highly hygroscopic disodium salt **4** with only 1 equiv of HCl, separation of sodium chloride, and purification of the monosodium (sulfinate) salt **7**, to the extent that this was

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(1) The previous papers on sulfinic acid derivatives related to research now planned that are considered as parts 1–11 in this series are as follows: (a) Field, L.; Grunwald, F. A. *J. Org. Chem.* **1951**, *16*, 946–953; (b) Field, L.; Hoelzel, C. B.; Locke, J. M. *J. Am. Chem. Soc.* **1962**, *84*, 847–850; (c) Field, L.; Locke, J. M.; Hoelzel, C. B.; Lawson, J. E. *J. Org. Chem.* **1962**, *27*, 3313–3315; (d) Field, L.; Parsons, T. F.; Crenshaw, R. R. *Ibid.* **1964**, *29*, 918–921; (e) Field, L.; Lacefield, W. B. *Ibid.* **1966**, *31*, 599–601; (f) Field, L.; Barbee, R. B. *Ibid.* **1969**, *34*, 1792–1798; (g) Field, L.; Hanley, W. S.; McVeigh, I. *J. Med. Chem.* **1971**, *14*, 995–996; (h) Field, L.; Khim, Y. H. *Ibid.* **1972**, *15*, 312–315; (i) Khim, Y. H.; Field, L. *J. Org. Chem.* **1972**, *37*, 2714–2720; (j) Srivastava, P. K.; Field, L. *Ibid.* **1972**, *37*, 4196–4198. (k) Srivastava, P. K.; Field, L; Grenan, M. M. *J. Med. Chem.* **1975**, *18*, 798–802.

(2) Abstracted from part of the Ph.D. Dissertation of V.E., Vanderbilt University, May 1981, which can be consulted for further details.

(3) Detoni, S.; Hadzi, D. *J. Chem. Soc.* **1955**, 3163–3169.

(4) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70–77.

(5) Collier, H. B. *Anal. Biochem.* **1973**, *56*, 310–311.

0022-3263/81/1946-2025$01.25/0

Table I. Polysulfides from 1,2-Dithiane 1,1-Dioxide (2)

| n sought for $Na_2S_n$ | value of $m$ in $[NaO_2S(CH_2)_4]_2S_m$ | | value of $X$ in $[NaO_2S(CH_2)_4]_2S_m \cdot XH_2O$[b] | initial TLC $R_f$[c] | behavior in $H_2O$ solution (25 °C) | | |
|---|---|---|---|---|---|---|---|
| | | | | | time for first change in | | |
| | sought | found[a] | | | appearance | TLC | $R_f$ (time)[c] |
| 1[d] | 3[d] | 3.0[d] | 2[d] | 0.69 | >1 week | >1 week | 0.69 (1 week) |
| 11[e] | 13[f] | 5.1[g] | 0.5 | 0.74 | 1 h[h] | 2 h | 0.62, 0.69, 0.74 (2 h) |
| 5 | 7 | 5.5[g] | 0.2 | 0.74 | 1 h[h] | 2 h | 0.62, 0.69, 0.74 (2 h) |
| 4 | 6 | 5.8 | 0.2 | 0.75 | 1 h[h] | ~48 h | 0.62, 0.70 (48 h) |
| 4[i] | 6[i] | 4.9[i] | 0.2[i] | 0.75 | 1 h[h,i] | ~48 h[i] | 0.62,[i] 0.69 (trace) (48 h) |
| 3 | 5 | 4.4 | 0.2 | 0.74 | 2 h[j] | ~48 h | 0.62, 0.70 (48 h) |
| 2 | 4 | 3.5 | 0.4 | 0.62, 0.69[k] | >48 h[l] | >48 h | 0.62, 0.69 (48 h) |

[a] By analysis for S; dried sample. [b] Determined by analysis. [c] Solvent system 1:1 MeOH–$Me_2CO$. [d] Prepared by the procedure of ref 1h. After 1 week at 25 °C, the IR spectrum of the solid trisulfide was unchanged, and a solution in $H_2O$ showed an unchanged $R_f$ (0.69) and no cloudiness whatsoever. [e] When 1 equiv of $Na_2S$ was treated with 10 molar equiv of S in MeOH, only 5.4 mol of S dissolved, thus giving $Na_2S_{6.4}$. The undissolved S was separated by centrifugation and identified by melting point and mixture melting point. Hence $n$ actually was 6.4. [f] Based on the actual value of $n$ as 6.4; the theoretical value of $m$ actually was 8.4. [g] A yellow solid, identified as S by melting point, mixture melting point, lack of IR, and solubility, had separated from the solution at the end of the reaction time of 2 h. [h] Separation of sulfur from a cloudy solution after 1 h; characterized by melting point, mixture melting point, solubility, and lack of IR. [i] See Experimental Section for details. [j] Cloudy solution after 2 h. [k] The IR spectrum suggested that considerable trisulfide 3 ($m$ = 3) was present (strong absorption ~1000 $cm^{-1}$; see Experimental Section). [l] Clear solution even after 2 days.

achievable by fractional precipitation, gave 7 (56%) as a nonhygroscopic presumed trihydrate. Although satisfactory elemental analyses could not be obtained for 7 (vide infra), consistent spectra and an SH content of at least 66% suggest sufficient purity of the 7 for most practical uses. The salt 7 could be converted to the analytically pure *S*-benzylthiouronium salt 8 in 70% yield; a molecular weight showed that the thiol group of 8 had not become oxidized thereby to the disulfide. A cerium(III) salt (13) also could be prepared in good yield; however, although the IR spectrum was satisfactory, sparing solubility precluded purification. Since 1,4-butanedisulfinic acid is a stable crystalline solid,[6] atypically for aliphatic sulfinic acids,[6] we converted the disalt 4 to the mercaptosulfinic acid 6; however, 6 proved to be an oil. The foregoing results suggest that mercaptoalkanesulfinates probably can be best used as synthons either as the disalt or as the monosalt or mercapto acid prepared in situ by acidification of a solution of the disalt in methanol and removal of the inorganic salt. Should purification of an intermediate appear desirable, however, it seems likely that the thiouronium salt might be isolated, dissolved in water, made basic, and extracted to leave a mono- or disalt of the synthon. To the best of our knowledge, no mercaptoalkanesulfinate has been reported previously.

Stability of the trisulfide 3 ($m$ = 3) in aqueous solution (Table I) prompted an effort to learn the extent to which the chain of sulfur atoms could be extended. Reactions of the dioxide 2 thus were studied with sodium polysulfides ($Na_2S_n$), nonstoichiometric compounds that were prepared as usual by dissolving ($n$ − 1) proportions of sulfur in one proportion of methanolic sodium sulfide. Table I shows the results.

In the synthesis of variants of 3 with $m$ exceeding 3 (Scheme I), possibilities were explored with $m$ as high as 13. In an effort to obtain 3 ($m$ = 13), however, only enough sulfur could be dissolved under the conditions used to give $Na_2S_{6.4}$. This $Na_2S_{6.4}$ in principle could produce 3 ($m$ = 8.4), i.e., a mixture of octa- and nonasulfides. In fact, however, elemental sulfur precipitated during the reaction with 2, suggesting that an initial polysulfide formed but then lost sulfur; the product had $m$ = 5.1 and evidently was largely the pentasulfide (Table I). An effort to prepare 3 ($m$ = 7) also led to precipitation of sulfur during the reaction and to a product like the first ($m$ = 5.5). The pentasulfide, or possibly the hexasulfide, thus seems to be as high as one can go with this system (i.e., 3, $m$ = 5–6). Two experiments directed toward the hexasulfide (3, $m$ = 6) gave $m$ = 5.8 (the highest value found) and 4.9. Accordingly, it appears that one *can* synthesize the polysulfides 3 with $m$ = 5–6 by effecting the reaction of Scheme I with 2 in methanol and precipitating the polysulfide as soon as reaction is complete by using acetone. Insolubility of sulfur in methanolic $Na_2S$ thus obviously precluded $m$ > 8.4, but, in fact, loss of sulfur during reaction actually precluded $m$ > 5–6.

Indeed, for stability in water exceeding a few hours, the practical limit of catenated sulfur atoms appears to be the tetrasulfide (3, $m$ = 4). Even though Table I indicates that 3 with $m$ = 5–6 can be prepared, such products lost sulfur slowly in aqueous solution. The tetrasulfide (3, $m$ = 4), on the other hand, evidently is stable in water for over 48 h and also was the highest polysulfide that gave clean TLC separation (cf. Table I, $m$ = 3.5); the $R_f$ value was 0.62, which compares with $R_f$ 0.69 for the trisulfide (3, $m$ = 3) and about 0.74 for the inseparable higher polysulfides (3, $m$ > 4), which showed considerable streaking. The behavior where $m$ exceeded 4 can be illustrated with 3 ($m$ = 4.9). This product was prepared and purified by the procedure used previously for the trisulfide (3, $m$ = 3).[1h] Elemental analysis for sulfur pointed to nearly pure pentasulfide (Table I), although tetrasulfide no doubt also was present. Dissolution of this product in water led to de-

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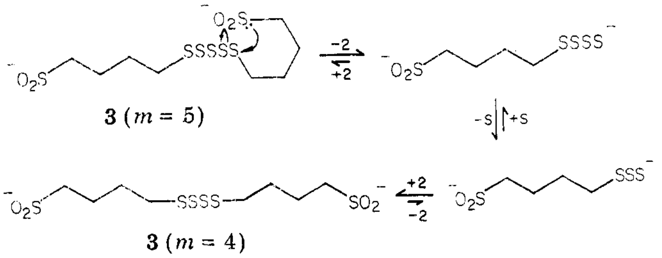
(6) Beachem, M. T.; Shaw, J. T.; Sargent, G. D.; Fortenbaugh, R. B.; Salsbury, J. M. *J. Am. Chem. Soc.* 1959, *81*, 5430–5435.

Scheme II



position of sulfur, which began after ~1 h and continued for about 48 h. Removal of sulfur and freeze–drying then gave solid which was shown to be the tetrasulfide disulfinate **3** ($m$ = 4) by TLC ($R_f$ 0.62), IR, and elemental analysis. With the assumption that the initial product was **3** ($m$ = 5), the loss of sulfur and formation of **3** ($m$ = 4) can be explained by Scheme II, in which the equilibria favor **3** ($m$ = 4) as the more stable species; even so, the TLC data of Table I suggest that a little trisulfide (**3**, $m$ = 3) usually accompanies the tetrasulfide. The polysulfides with $m > 5$ presumably lose sulfur and go to **3** ($m$ = 4) by similar paths. The neighboring-group effect of $SO_2Na$ thus appears to operate much as it does with disulfide sulfinates.[1i–k]

It is worth adding that the IR spectra of the polythiobis(butanesulfinates) looked astonishingly like what one might expect for sulfonates; that the spectra indeed represented sulfinates, however, was shown in a variety of ways (see Experimental Section). Absorption occurred for $SO_2Na$ at ~1070 $cm^{-1}$ and perhaps at ~1180 and/or ~1020 $cm^{-1}$.

Although the reactions modeled in Scheme I promise to be quite useful, past and present experience suggest several conclusions likely to be helpful in working with them. (a) Oxidation of SH to SS or of $SO_2Na$ to $SO_3Na$ should be guarded against, although reasonable care seemed to preclude major problems. (b) Polysulfides of type **3** with $m > 5$ are likely to lose sulfur during preparation, and those with $m > 4$ are likely to do so in aqueous solution as well. (c) Polysulfides of type **3** with $m > 4$ cannot be practicably separated because the considerations in b preclude prolonged chromatography, because $R_f$ values are nearly identical in TLC, and because fractional precipitation is probably only marginally effective. Best success with fractional precipitation, it might be added, has been obtained by dissolution in a solvent such as methanol, precipitation and removal of ~10% of the original amount by using a solvent such as ether or acetone (probably better; see Experimental Section for **7**), and further precipitation of ~80% of the original amount, leaving ~10% in solution. (d) Analyses of sulfinates often are complicated by variable hydration and the difficulty (or impossibility) of dehydrating them completely without decomposing the sulfinate. Illustratively, one sample of an earlier (anhydrous) sulfinate in analyses by three laboratories showed standard deviations in results as follows (in percent): C, 1.40; H, 0.71; N, 0.23; Na, 0.87; O, 2.46; S, 3.42.[1g]

## Experimental Section

Melting points were determined by using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra, reported in parts per million ($\delta$), were obtained with a JEOL Model JNM-MH-100 spectrometer with $Me_4Si$ as an internal standard [or, in $D_2O$, with $Me_3Si(CH_2)_3SO_3Na$]. IR spectra were obtained by using Nujol mulls or KBr pellets with a Perkin-Elmer 727 spectrometer: s = one of the 3 or 4 strongest bands; m = ~$^1/_3$ to $^2/_3$ the intensity of s; all other bands were weaker than m. Elemental analyses were performed by Galbraith Laboratories. Moist extracts usually were dried by using anhydrous $MgSO_4$, and the solvent was then removed under aspirator pressure with a rotary-flask evaporator. TLC of reaction products was performed on Eastman Chromagram No. 6060 silica gel sheets with fluorescent indicator; spots were detected by using UV light or $I_2$ vapor; streaking occurred with the polysulfides (**3**, $m > 4$), and not too much weight should be attached to these values. 1,2-Dithiane 1,1-dioxide (**2**) was prepared by converting 1,4-butanedithiol to 1,2-dithiane (yields, ~84–90%) with $p$-toluenesulfonyl chloride and then oxidizing the dithiane with aqueous $KIO_4$ (yields, ~15–31%), all essentially as described.[7] Except as otherwise referenced, all other materials were commercial products. Feigl tests were done conventionally with $I_2$–$NaN_3$ reagent,[8] a positive test being considered immediate decolorization and vigorous evolution of $N_2$. For determinations of SH by the Ellman technique,[4] known volumes of the thiol solutions were added to an excess of Ellman's reagent (**11**) in a phosphate buffer solution (pH 8.0, $\mu$ = 0.1), and adsorptions were recorded against a reagent blank by using a Bausch and Lomb Spectronic 20 spectrophotometer at 412 nm; calculations of the percent thiol were based on $\epsilon_{max}$ = 13 600 L $mol^{-1}$ $cm^{-1}$, Ellman's value; $^4\epsilon_{max}$ has been reported to range from 11 900 ± 600 to 14 140 ± 170.[5]

**Reduction of 1,2-Dithiane 1,1-Dioxide (2) (and of Dibenzo[*c,e*][1,2]dithiin 5,5-Dioxide, 9).** The dioxide **2** (0.50 g, 3.3 mmol) dissolved in 15 mL of THF was added to 75 mL of freshly distilled liquid ammonia in a three-necked flask chilled in dry ice and acetone and equipped with a dry ice condenser and gas-inlet tube. The mixture was stirred, and sodium (0.152 g, 0.0066 mol) was added in small pieces during 1 h. The solution was stirred for an additional 45 min. A white solid precipitated. Ammonia and THF then were swept away by using a steady stream of Ar. The residue was the very hygroscopic disodium 4-mercaptobutanesulfinate (**4**): 0.64 g (99%); IR (KBr) 3600–2800 (s, br), 1650–1620, 1460 (m), 1400 (m), 1020 (s), 970 (s), 730 $cm^{-1}$; NMR ($D_2O$) $\delta$ 2.9–2.6 (m, ~1 H), 2.6–2.2 (m, ~3 H), 1.8–1.4 (m, 4 H). Assay by the Ellman technique showed at least 67% of expectation for thiol content, hence the yield of **4** was at least 66%.

The dioxide **9** (0.50 g, 2.01 mmol)[1k] was reduced to the very hygroscopic disodium 2-mercapto-2′-biphenylsulfinate (**10**; 0.58 g, 93%) by the procedure used with **2**: IR (KBr) 3600–2800 (s, br), 2650, 1620–1600 (m), 1440 (m), 1420 (m), 1110 (m), 1010 (s), 960 (s), 740 (s), 700 (m) $cm^{-1}$. The IR band at 1310 $cm^{-1}$ of **9** (assigned to $SSO_2$)[1k] disappeared completely and none was seen at 1080–1025 $cm^{-1}$ (characteristic of the oxidation product, $SO_3Na$).[9] Also consistent with formation of **10** was the great solubility in water but insolubility in organic solvents, decolorization of aqueous $KMnO_4$, a strongly positive Feigl test with $I_2$–$NaN_3$, and 1.3 equiv of thiol function found by the Ellman technique (cf. the previous discussion).

Other reductions of **2** were unpromising. Sodium hydride, ineffective alone,[1h] could not be solubilized by using dibenzo-18-crown-6 or dicyclohexano-18-crown-6 in DMF (use of NaH with an alkoxide–metallic salt was not explored because of the probability of difficultly separable products).[10] For reduction of **2** by $NaBH_4$, a solution of $NaBH_4$ (0.64 g, 16.9 mmol) in absolute EtOH (40 mL) was added dropwise to one of **2** (0.80 g, 5.3 mmol; 20 mL of EtOH). Gas evolution started immediately, and white solid separated. After the mixture was stirred for 4 h, the solid (0.67 g) was separated, dried (0.5 mm), dissolved in $H_2O$ (3 mL), and acidified with 10% HCl. The white precipitate was combined with identical solid obtained by evaporating and acidifying the ethanol filtrate: yield 0.56 g; virtually insoluble in all solvents tried, including $H_2O$; mp 74–77 °C; IR (KBr pellet) 2950 (s), 2850 (s), 2500–2300 (s, br), 1660–1640, 1440 (m), 1400 (m), 1320 (m), 1280 (m), 1120 (m), 1060 (s), 1010 (s), 840 (s), 720, 640 $cm^{-1}$.

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[7] Field, L.; Barbee, R. B. *J. Org. Chem.* **1969**, *34*, 36–41.

[8] Feigl, F. "Spot Tests in Organic Analysis"; Elsevier: New York, 1960; pp 242–245.

[9] Colthup, N. B.; Daly, L. H.; Wiberly, S. E. "Introduction to Infrared and Raman Spectroscopy"; Academic Press: New York, 1964; pp 310, 360.

[10] Mordenti, L.; Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1979**, *44*, 2203–2205.

Anal. Calcd for $[S(CH_2)_4SO_2{\cdot}0.5H_2O]_n$: C, 29.8; H, 5.6; S, 39.8. Found: C, 31.7; H, 6.0; S, 39.5; B, <0.5.

**Conversion of the Disodium Salt 4 to 4-[(2,4-Dinitrophenyl)thio]butyl 2,4-Dinitrophenyl Sulfone (5).** The disodium salt 4 (0.40 g, 2.0 mmol) dissolved in 12 mL of EtOH was added to a solution of 2,4-dinitrochlorobenzene (0.73 g, 3.6 mmol) in 4 mL of EtOH. A yellow precipitate appeared immediately. The suspension then was heated under reflux for 19 h. The yellow solid, 5, then was separated from the solution by centrifugation, washed with benzene (2 × 15 mL), cold $H_2O$ (2 × 10 mL), and hot $H_2O$ (2 × 10 mL), and dried (0.5 mm, 12 h). Two recrystallizations from $Me_2CO$ gave 0.53 g (61%) of 5 as yellow crystals with a constant melting point of 185–186 °C: IR (KBr) 3100, 1590 (s), 1540 (s), 1500 (s), 1360–1340 (s), 1300 (m), 1240, 1150 (s), 1100, 1050, 1020–1000, 910, 830 (m), 740 (s) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 8.9 (s with a shoulder, 2 H), 8.7 (m, 1 H), 8.4 (m, 2 H), 7.8 (m, 1 H), 3.2 (m, 4 H), 1.8 (m, 4 H).

Anal. Calcd for $C_{16}H_{14}N_4O_{10}S_2$: C, 39.5; H, 2.9; S, 13.2. Found: C, 39.6; H, 2.9; S, 13.3.

**4-Mercaptobutanesulfinic Acid (6) and Monosulfinate Salts.** For preparation of ***S*-benzylthiouronium 4-mercaptobutanesulfinate (8)**, a solution of the disodium salt 4 (0.628 g, 3.17 mmol) in 20 mL of EtOH was treated with concentrated HCl (0.263 mL, 3.17 mmol) at 0 °C. Precipitated NaCl was separated by centrifugation, and the EtOH was evaporated to leave a semisolid. The semisolid (0.58 g) was dissolved in 8 mL of $H_2O$, and 3 drops of 0.1 N HCl were added to make the solution slightly acidic.[11] To this solution was added *S*-benzylthiouronium chloride (1.00 g, 4.93 mmol) dissolved in 5 mL of $H_2O$. The white solid 8 that precipitated was separated, washed with cold $H_2O$, and dried. Two recrystallizations from $H_2O$ gave 0.71 g (70%) of 8 as white crystals with a constant melting point of 151–152.5 °C: IR (KBr) 3250–2300 (s, br), 1670 (m), 1560, 1490, 1450 (m), 1420 (m), 1250, 1130, 1070, 1010 (sh,m), 990–960 (s, 3 bands), 720 (m), 690 $cm^{-1}$; NMR (MeOH-$d_4$) $\delta$ 7.3 (s, 5 H), 4.4 (s, 2 H), 2.65 (t, 2 H), 2.3 (m, 2 H), 1.75 (m, 4 H).

Anal. Calcd for $C_{12}H_{20}N_2O_2S_3$: C, 45.0; H, 6.3; mol wt 320. Found: C, 44.8; H, 5.6; mol wt (MeOH) 303.

Storage at 0 °C for ~1 year caused a crude sample to decrease from a minimum thiol content of 65% to 23%.

Although **sodium 4-mercaptobutanesulfinate (7)** could be isolated, satisfactory elemental analyses could not be obtained. For the isolation, absolute EtOH (80 mL) was added to the disodium salt 4 (5.20 g, 26.3 mmol), freshly prepared from the $Na/NH_3$ reduction of 2, and the solution was cooled to 0 °C. Concentrated HCl (2.2 mL, 12 N, 26.4 mequiv) then was added, and the NaCl that precipitated was separated by centrifugation. Addition of $Me_2CO$ (~260 mL) and then of $Et_2O$ (~160 mL) at 0 °C to the EtOH solution gave a pale yellow precipitate (each was added until precipitation seemed complete). Yellow precipitate 7 then was separated by centrifugation and dried (3.4 g, 56%, calcd as $7{\cdot}3H_2O$). This 7 was dissolved in MeOH (~15 mL), and dry $Me_2CO$ was added until cloudy precipitate began to appear. A colorless clear solution then resulted upon removal of the small amount of precipitate (an estimated 10–20% of the total solid) by centrifugation as quickly as possible. Dry $Me_2CO$ again was added to this solution until the appearance of white precipitate was complete (leaving an estimated 10–20% unprecipitated). The white precipitate was separated by centrifugation and dried at 25 °C for 12 h: yield 2.6 g (43%, calcd as $7{\cdot}3H_2O$); mp, sinters at 110 °C, dec at 195 °C; IR (KBr) 3600–2400 (s, br), 1650–1620, 1460 (m), 1400 (m), 1000 (s), 970–960 (s), 730 $cm^{-1}$; NMR ($D_2O$) $\delta$ 2.8–2.6 (t, 2 H), 2.5–2.2 (m, 2 H), 1.9–1.5 (m, 4 H); TLC (MeOH) of the 7 showed one strong spot at $R_f$ 0.7 but also two other weak ones. Ellman's reagent showed at least 66% of the calculated SH. Solvation proved to be even more vexing than usual with sulfinates (loss on heating to constant weight, 28.2–31.0%; calcd for $7{\cdot}3.H_2O$, 23.5%; $7{\cdot}4H_2O$ (calcd for $H_2O$, 29.0%) was excluded on the basis of the percent S found (26.7% and 27.9%; calcd for $7{\cdot}3H_2O$, 27.8%; calcd for $7{\cdot}4H_2O$, 25.8%). The possibility of partial acetone solvation (high carbon analyses) was excluded by NMR; however; a peak at $\delta$ 3.6 (~0.5 H, m) was consistent with some solvation by $Et_2O$, suggesting that $Me_2CO$ is better for precipitation. The $7{\cdot}3H_2O$ showed a surprising lack of hygroscopicity and remained as a free-flowing solid under ambient conditions in the open for 1 week; it then showed no decrease in the Ellman value for SH.

The properties of **4-mercaptobutanesulfinic acid (6)** were explored by adding 0.071 mL (0.85 mequiv) of 12 N HCl to a solution of 0.15 g (0.65 mmol) of $7{\cdot}3H_2O$ in 1.5 mL of MeOH at 0 °C, removing NaCl by centrifugation, and then removing MeOH under vacuum; 6 was obtained as an oil that showed no tendency toward crystallization but gave strong Feigl and Ellman reactions.

**A cerium(III) salt of 6** apparently resulted when cerium nitrate hexahydrate (0.17 g, 0.39 mmol) in $H_2O$ (2 mL) was added to $7{\cdot}3H_2O$ (0.20 g, 0.87 mmol) in 2 mL of $H_2O$. The white solid (13) that precipitated immediately was separated, washed, and dried; it then amounted to 0.23 g and darkened slightly without melting at 230 °C. Virtual insolubility ($H_2O$, alcohols, $CHCl_3$) precluded purification, and meaningful analyses could not be obtained [dried at 25 °C for 4 h (0.5 torr): C, 21.8; H, 4.5; S, 23.6. After vigorous drying: S, 22.7; $H_2O$, 2.8]. However, 13 gave a positive Feigl test, decolorized aqueous $KMnO_4$, and had a IR spectrum consistent with 13 as a cerium salt of 6: IR (KBr) 3500–3100 (s), 2950 (m), 2870, 2650, 2450, 1630, 1580, 1420 (s), 1400–1380 (s), 1220, 1170, 1000 (s), 980–960 (s, 3 bands), 810, and 740 $cm^{-1}$.

**Preparation and Reactions of Disodium 4,4'-Polythiobis(butanesulfinates) (3).** The preparation of 3 ($m$ = 4.9) illustrates the general procedure. Sulfur (1.2 g, 0.0374 mol) was added to a solution of $Na_2S{\cdot}9H_2O$ (3.0 g, 12.5 mol) dissolved in MeOH (60 mL). This solution then was added slowly to the dioxide 2 (4.1 g, 27 mmol) in MeOH (30 mL) at 0–5 °C with good stirring under Ar during 2 h. After the addition, the pH of the solution was 7. Addition of $Me_2CO$ (250 mL) and then of $Et_2O$ (400 mL) at 0 °C to the reaction mixture gave a white precipitate (each was added until precipitation seemed complete). White precipitate 3 ($m$ = 4.9) then was separated by centrifugation and dried [yield (as 3 ($m$ = 4.9)$\cdot$0.2$H_2O$) 4.9 g, 88%]. This 3 ($m$ = 4.9) was dissolved in MeOH (15 mL), and dry $Me_2CO$ was added until a cloudy precipitate (an estimated 10% of the total) began to appear. A colorless clear solution then resulted upon removal of the small amount of solid by centrifugation as quickly as possible. Dry $Me_2CO$ again was added to this solution until the appearance of white solid was complete (an estimated 10–15% remained unprecipitated). This solid then was separated by centrifugation and dried at 0.5 mm for 12 h at 25 °C: yield (as 3 ($m$ = 4.9)$\cdot$0.2 $H_2O$) 4.0 g (72%); mp 200 °C dec; IR (KBr) 3650–3000 (s), 2950 (s), 2900 (s), 2650, 1620, 1440, 1400 (m), 1280 (m), 1220 (m), 1180–1160 (s), 1100, 1080–1060 (s), 1020 (m), 980 (m), 770 (s), 740, 700 $cm^{-1}$.

Anal. Calcd for $C_8H_{16}Na_2O_4S_{6.9}{\cdot}0.2H_2O$: C, 21.5; H, 3.7; S, 49.5; $H_2O$, 0.8. Found: C, 20.0; H, 3.6; S, 50.0 (average of 49.3 and 50.6 on same sample); $H_2O$, 0.9.

The behavior of the polysulfides in solution also can be illustrated with 3 ($m$ = 4.9). Compound 3 ($m$ = 4.9) (0.60 g, 1.34 mmol) dissolved readily in $H_2O$ (15 mL) to give a completely clear solution. Within 1 h, solid began to separate. Four times within 48 h accumulated yellow solid was separated by centrifugation, washed well ($H_2O$, $Me_2CO$, and $Et_2O$), and dried; each solid was identified as sulfur by a melting point and mixture melting point within the range of 116–119 °C, by solubility in $CS_2$ but not significantly in other solvents, and by lack of IR absorption; sulfur was similarly identified in most of the other experiments where Table I notes its formation. Precipitation had virtually ceased after 48 h, at which time the clear solution was freeze–dried; 0.51 g [92% of 3 ($m$ = 4)]. The IR (KBr) was congruent with that of the starting material; absence of the very strong peak centered at ~1000 $cm^{-1}$, which seems characteristic of 3 with $m$ = 2 or 3, suggested that little disulfide or trisulfide was present (3, $m$ = 2, 3). The TLC $R_f$ (1:1 MeOH–$Me_2CO$) was 0.62 (with a faint spot of trisulfide at 0.69), consistent with assignment of $R_f$ 0.62 to tetrasulfides in Table I; the $R_f$ for the higher polysulfides of Table I seemed to be ~0.74. The freeze–dried product was dried further at 0.5 mm for 24 h at ~25 °C.

Anal. Calcd for $C_8H_{16}Na_2O_4S_6$: S, 46.4. Found: S, 46.7.

Table I gives details for the other polysulfides studied. All IR spectra were congruent with that of 3 ($m$ = 4.9)$\cdot$0.2$H_2O$, except

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[11] Kurzer, F.; Powell, J. R. *J. Chem. Soc.* **1952**, 3728–3734.

[12] Ref 9, pp 285, 308.

that of the lowest polysulfide (**3**, $m = 3.5$). The latter had its strongest band centered at $\sim$1000 cm$^{-1}$ in common with the di- and trisulfide (**3**, $m = 2, 3$);[1h] this band became inconspicuous when $m$ exceeded 3. Hence **3** ($m = 3.5$) evidently contained considerable trisulfide. Astonishingly, all of the polysulfide spectra showed strong bands at 1230–1120 and 1080–1025 cm$^{-1}$ characteristic of sulfonate salts.[9] The extreme improbability that significant oxidation had occurred of $SO_2Na$ to $SO_3Na$, however, followed from several facts: (a) presence of such bands in the analytically pure trisulfide **3** ($m = 3$) but not in the disulfide;[1h] (b) the improbability of equivalent oxidation that would produce *congruent* polysulfide (disulfinate) spectra; (c) the lack of exposure to $O_2$ or oxidants (Ar-purged solvents, Ar atmosphere), together with the short time from the beginning of reaction to the final product (<6 h); (d) resistance to oxidation of aqueous solutions of the disulfinate **3** ($m = 3$) under ambient conditions in excess of 1 week (Table I); (e) the facile loss of sulfur (cf. Scheme II), which contrasts with the stability of a sulfonate disulfide ($AcNH(CH_2)_2SS(CH_2)_4SO_3Na$; trace of disproportionation to symmetrical disulfides in 96 h at 61 °C) but accords with that of a sulfinate disulfide ($AcNH(CH_2)_2SS(CH_2)_4SO_2Na$; $\sim$50% disproportionation in 0.5 h at 61 °C).[1i] Nevertheless, for certainty, the identity of **3** ($m = 4.9$) as a sulfinate was confirmed in two ways. (a) An aqueous solution of **3** ($m = 4.9$) was treated with 6 equiv of 30% aqueous $H_2O_2$ and a trace of HCl, allowed to stand for 1 h, neutralized, and freeze-dried. Absence of the strong band at 1070 cm$^{-1}$ in this resulting solid showed oxidation of $SO_2Na$ to $SO_3Na$ and confirmed assignment of the band at 1070 cm$^{-1}$ to $SO_2Na$; loss of the band at 1020 cm$^{-1}$ appeared to occur but was less clear. Strong bands appeared in the product at 1230–1120 and 1090 cm$^{-1}$, as expected for $SO_3Na$.[9] (b) Reflux of **3** ($m = 4.9$) with 2 equiv of 2,4-dinitrochlorobenzene for 3 h in EtOH led to a yellow precipitate having the strong bands characteristic of a nitrosulfone [1530–1500 ($NO_2$), 1360–1320 (3 bands; $NO_2$, $SO_2$), 1140 cm$^{-1}$ ($SO_2$)].[12] Absence again of the 1070-cm$^{-1}$ band of **3** ($m = 4.9$), through conversion of $SO_2Na$ to $SO_2Ar(NO_2)_2$, confirmed the assignment to $SO_2Na$; the 1180-cm$^{-1}$ band also had disappeared and perhaps also that at 1020 cm$^{-1}$. Hence the IR bands for polythiobis(butanesulfinates) include that at 1070 cm$^{-1}$ and perhaps 1180 and/or 1020 cm$^{-1}$.

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**Registry No. 2**, 18321-15-8; **3** ($m = 3$), 56527-86-7; **3** ($m = 4$), 76832-43-4; **3** ($m = 5$), 76832-44-5; **3** ($m = 6$), 76832-45-6; **4**, 76832-46-7; **5**, 76832-47-8; **6**, 76832-48-9; **7**, 76832-49-0; **8**, 76832-50-3; **9**, 25331-82-2; **10**, 76832-51-4; **13**, 76832-52-5; sodium polysulfide, 1344-08-7; 2,4-dinitrochlorobenzene, 97-00-7; *S*-benzylthiouronium chloride, 538-28-3.

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# Metalated Unsaturated Amides. Regio- and Stereoselective γ-Alkylation[1,2]

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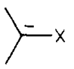
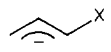
The reactions of lithiated and dilithiated unsaturated amides **4**, **5**, **12**, **15**, **18**, **34**, and **36** with a variety of electrophiles have been shown to produce deconjugated, $\alpha$-alkylated products **6**, **7**, **13**, **16**, **19**, **35**, and **37**, respectively, in good to excellent yields (Tables I, II, IV, and VI). Whereas lithiated **4** and dilithiated **5** do not undergo $\gamma$-alkylation, the corresponding species of **12** and **15**, when converted to their cuprates by using cuprous iodide, afford $\gamma$ products **4** and **17** with good regio- (67–90%) and *Z* stereoselectivity (67–80%) for E = allyl, prenyl, and geranyl. Differences between the reactions of cuprated, unsaturated amides and unsaturated carboxylic acids with nonallylic alkylating agents are discussed. The reaction of dicuprated *N*-methylsenecioamide (**15**) with prenyl bromide leads to a complex mixture of products which have been separated and characterized (Scheme III). The reaction of lithiated *N*,*N*-dimethylsenecioamide (**18**) with aromatic and pyridine aldehydes and some ketones has been shown to provide $\alpha$ (**19**) or $\gamma$ (**20**) products, depending on the conditions of the reaction (Table VI). In this reaction, the reversible formation of the $\alpha$ product **19** and its conversion into the $\gamma$ product **20** have been demonstrated (Scheme IV). The utility of the $\alpha$- and $\gamma$-alkylated unsaturated amide products is illustrated by the syntheses of the monoterpenoid lavandulol (**42**) and the amide alkaloid piperlonguminine (**43**), respectively.

Carbon–carbon bond formation by alkylation of charge-stabilized carbanions of the type **1** ($d^2$ reagents)[3] is a fundamental organic reaction whose synthetic utility has been revolutionized in recent years by the availability of strong bases and chelating or basifying solvents[4,5] which allow great latitude in the conditions under which species **1** may be derived.[6] Dimetalated carboxylic acids, already



**1**



**2**

X = CHO, COR, CH=NR, CH=NNR$_2$, CN, CO$_2$R, CO$_2^-$, CONR$_2$, CON$^-$R

recognized by Grignard in 1904 and extensively investigated by Ivanov,[7] have had a considerable impact in synthetic practice.[8] Metalated carboxamides, on the other hand, although first described by Hauser[9] as part of his

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