3.42; S, 23.48. Found: C, 35.37; H, 5.40; N, 3.25; S, 23.28.

**Compounds Related to 1,2-Dithiolane-4-carboxylic Acid (16).**[17] **A. 16** *via* **$H_2O_2$.**—The acid **15** (15.2 g, 0.10 mol) in AcOH (150 ml) and $H_2O_2$ (11.5 g of 30%, 0.1 mol) in AcOH (150 ml) were added simultaneously from two dropping funnels to AcOH (100 ml) containing KI (0.418 g, 0.00251 mol; as a catalyst) at 75° during 3 hr. After 10 min at 25° (starch–KI test negative), most of the AcOH and $H_2O$ were removed at 40° (20 mm). The residue was extracted with $Et_2O$ and benzene. The extracts were combined, dried, and evaporated to a greasy solid, yield 10.2 g (68%), mp 63–70°. This solid was extracted carefully with benzene at 25°. Removal of benzene gave yellow, crystalline **16**: yield 8.5 g (57%; yields up to 85% were obtained on a smaller scale); mp 75–76° (lit.[8] mp 76.5–77.5°); nmr ($CDCl_3$) $\delta$ 3.5 (m, $CH_2$ and CH), 12.3 (s, $CO_2H$).

**B. 16** *via* **$I_2$–$Et_3N$.**—A solution of **15** (0.76 g, 5.0 mmol) and $Et_3N$ (1.04 g, 10.3 mmol) in MeOH (15 ml) was added to one of $I_2$ (1.28 g, 5.0 mmol) in MeOH (30 ml) at 25° during 10 min. Benzene (180 ml) then was added immediately. The organic layer was washed with 10% aqueous $Na_2SO_3$ solution to remove $I_2$, then with a little cold $H_2O$, and was dried. Removal of benzene left 0.30 g (40%) of yellow **16**, mp 76–78°.

**C. 16** *via* **$K_3Fe(CN)_6$.**—Aqueous solutions of $K_3Fe(CN)_6$ (16.6 ml of 1 *N*) and of KOH (6.5 ml of 2 *N*) were added to the sodium salt of **15** (1.0 g, 6.58 mmol) in $H_2O$ (5 ml); the pH was kept at ~7 (*cf.* ref 10). The mixture then was acidified with 2% aqueous HCl and was extracted with benzene. Removal of benzene left 0.32 g (32%) of yellow **16**, mp 73–75°.

**D. 1-Monoxide (17) of 16.**—A solution of $H_2O_2$ (0.113 g of 30% $H_2O_2$, 1.0 mmol) in 1 ml of $H_2O$ was added slowly to **16** (0.15 g, 1.0 mmol) in $H_2O$ (30 ml) at 5°, and the mixture was kept at 25° for 16 hr; a starch–KI test then was negative. Removal of $H_2O$ by freeze drying left white **17**: yield 0.12 g (72%); mp 100–102° (lit.[11] mp 104–110°); ir 1020 (SO) and 1725 $cm^{-1}$ (CO).

**E. Study of the Carbinol (19) Corresponding to Acid 16. 2-Mercaptomethyl-3-mercaptopropanol (18)** first was prepared by heating a mixture of the acid **15** (7.6 g, 50.0 mmol) in THF (700 ml) with $LiAlH_4$ (7.6 g, 200 mmol) in THF (100 ml) under reflux for 26 hr and then carefully hydrolyzing with $H_2O$ (40 ml) by heating for 2 hr. The mixture then was acidified with 5% aqueous HCl, and **18** was extracted with $Et_2O$. Drying and removal of solvent gave liquid **18**. Distillation gave 4.8 g (70%) of **18**: bp 90–91° (0.6 mm); $n^{25}{}_D$ 1.5606; nmr ($CDCl_3$) $\delta$ 1.43 (t, SH), 1.89 (m, CH), 2.70 (m, $CH_2SH$), 3.04 (s, OH), 3.72 (d, $OCH_2$); ir (neat) 3360, 2900, 2520, 1430, 1015 $cm^{-1}$.

*Anal.* Calcd for $C_4H_{10}OS_2$: C, 34.75; H, 7.25; S, 46.35. Found: C, 35.00, H, 7.17 S, 46.19.

For conversion of **18** to **4-hydroxymethyl-1,2-dithiolane (19)**, solutions of **18** (0.55 g, 4.0 mmol) and of $H_2O_2$ (0.45 g, 30%, 4.0 mmol) in AcOH (14 ml) were added simultaneously from separate dropping funnels to AcOH (8 ml)–$H_2O$ (12 ml) containing KI (17 mg) at 75° during 10 min with stirring (a starch–KI test then was negative). A benzene extract of the concentrated mixture was washed with 5% aqueous $Na_2CO_3$ solution and then with $H_2O$, dried, and concentrated; yield of presumed (impure) liquid **19**, 0.38 g (70%). Ir spectra were consistent with the assignment of structure **19** (the pale yellow benzene-soluble product polymerized to a gum, insoluble in benzene, in ~10 hr and began to polymerize even in ~2–3 hr at 25°): ir (neat) 3480, 2920, 1470, 1410, 1250, 1035, and 670 $cm^{-1}$ [no SH absorption at 2520 $cm^{-1}$; the ir spectrum of **19** resembled that of **18** and did not have the flattened-out appearance expected of a polymer (*cf.* ref 11)].

Since **19** polymerized so readily, in the attempt to convert it to 1,2-dithiolanyl-4-carbinol 1,1-dioxide (**20a**), 0.38 g (2.80 mmol) of **19** immediately after its preparation was allowed to react with $H_2O_2$ (0.77 g, 30%, 6.8 mmol) in aqueous AcOH ($H_2O$, 10 ml; AcOH, 10 ml) at 75° for 20 hr with stirring. The mixture was concentrated and then extracted with $CHCl_3$. The removal of $CHCl_3$ after drying gave 0.10 g (16%, for **20b** not **20a**): ir 1740 (ester C=O),[18] 1430 ($CH_3$ of $CH_3CO$),[18] 1300 ($-SO_2-$), 1230 (AcO),[18] 1125 ($-SO_2-$), and 1050 $cm^{-1}$ (–CO–) (slight absorption, relative to **19**, at 3450 $cm^{-1}$ was attributed to an ester overtone and suggested little if any –OH);[18] nmr ($CDCl_3$) $\delta$ 2.12 [s, $CH_3C(O)$],[18] 3.7–2.7 (m, $-CH_2-$ and –CH–), 4.4–4.2 (m, $-CH_2-$) (no OH peak was observed).[18]

**Registry No.**—**6**, 34910-57-1; **7**, 34910-58-2; **8**, 34910-59-3; **9**, 34910-60-6; **10**, 34915-74-7; **11**, 34915-75-8; **14**, 34915-76-9; **16**, 2224-02-4; **17**, 3083-96-3; **18**, 34915-79-2; **20b**, 34934-76-4.

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[17] Wherever feasible, protection from light was effected using Al foil.

[18] These observations support the formulation of the product isolated as **20b** but are inconsistent with formulation as **20a**. The ir spectrum of the product impressed us as the type expected for a monomer, rather than the flattened-out type expected for a polymer (*cf.* ref 11).

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# Organic Disulfides and Related Substances. 35. Preparation of Unsymmetrical Disulfides Containing Carboxylate Moieties and Neighboring-Group Effects of Sulfinate and Carboxylate Moieties on Disproportionation[1a,b]

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The sulfinate salt $AcNH(CH_2)_2SS(CH_2)_4SO_2Na$ (**2**), upon disproportionation, reaches equilibrium with the two possible symmetrical disulfide products in ~0.5 hr in water at 61° ($K \cong 3$–6). The sulfone analog [$AcNH(CH_2)_2SS(CH_2)_4SO_2CH_2Ph$ (**5**)] and sulfonate analog [$AcNH(CH_2)_2SS(CH_2)_4SO_3Na$ (**6**)] do not disproportionate under these conditions. The marked acceleration with **2** *vis-à-vis* **5** and **6** is attributed to a neighboring-group effect of the $-SO_2^-$ moiety, which was further indicated by slower reaction of **2** in methanol (attributed to a tight ion pair) and by isolation of 1,2-dithiane 1,1-dioxide (**8**, 39% yield) in the presence of a thiol trap. Carboxylate analogs, $AcNH(CH_2)_2SS(CH_2)_nCO_2H$ (**11–14**, $n = 1$–4), were best prepared by thioalkylating $\omega$-mercapto acids with a thiolsulfonate (these analogs proved to be only slightly protective against ionizing radiation). The acids **11–14** resisted disproportionation. The salts **11′–14′** disproportionated fairly readily, but ($n = 4$) less readily than **2** by a factor of ~300. Neighboring-group acceleration of disproportionation in the carboxylate series is indicated by the difference in behavior of the salts **11′–14′** and the acids **11–14**, by a marked dependence of rapidity on the pH near neutrality, and by variations in rapidity from $n = 1$ (fastest) to $n = 2$, 3, or 4 (slower and comparable).

Earlier work showed that the aminosulfone salt **1** was among the most stable disulfides we have studied in resistance to disproportionation to two symmetrical disulfides (79% disproportionation at 100° in water after 72 hr.[2] To our surprise, sodium 4-(2-acetamidoethyldithio)butanesulfinate (**2**) disproportionated far

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[1] (a) Paper 34: L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1972). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA17-69-C-9128.

[2] L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).

$$\underset{\mathbf{1}}{Cl^{-}H_3N^{+}(CH_2)_2SS(CH_2)_4SO_2CH_2Ph}$$

more rapidly (~50%, 61°, water, 0.5 hr); the reaction appeared to reach equilibrium after ~55% disproportionation.[3] It seems likely that a neighboring-group effect of the sulfinate moiety ($-SO_2^-$) is responsible for this marked acceleration. This paper considers this matter and related ones. Similar increases with other disulfides have been attributed to neighboring-group participation of amino, acetamido, *o*-carboxylate, and perhaps to some extent other functional groups.[4]

Equation 1 shows the disproportionation of the sulfinate **2** to form the two symmetrical disulfides, 2-acetamidoethyl disulfide (**3**) and disodium 4,4′-dithiobis(butanesulfinate) (**4**). After the disproportionation of **2** in methanol, **3** was isolated in 50% yield; as previously reported,[3] several equilibrations with removal of **3** each time forced the reaction, giving what could only be **4** (consistent spectra); **4** could not be obtained entirely free of **3**, but elemental analyses nevertheless were satisfactory (C, H, S, and Na).[3]

$$\underset{\mathbf{2}}{2AcNH(CH_2)_2SS(CH_2)_4SO_2Na} \underset{}{\overset{H_2O\text{ or }MeOH}{\rightleftarrows}} \underset{\mathbf{3}}{[AcNH(CH_2)_2S]_2} + \underset{\mathbf{4}}{[NaO_2S(CH_2)_4S]_2} \quad (1)$$

In much of our earlier work, disproportionation of unsymmetrical disulfides has been nearly complete (for reasons such as virtual insolubility of one product) instead of reaching the usual equilibrium.[5] Since **2**, **3**, and **4** are soluble in water or methanol, however, it is not surprising that eq 1 represents an equilibrium.

Figure 1 shows that the per cent of disproportionation of **2** in water or methanol rises to ~50–55% and then remains constant. If ~53% is assumed to be the equilibrium value, the usual reverse sense of $\mathbf{3} + \mathbf{4} \rightleftarrows 2(\mathbf{2})$ would give $K \cong 3$ for eq 1, a value close to the statistical one of 4.[6] The reversibility of eq 1 was confirmed by equilibrating **3** and **4** and determining the amount of **2** by tlc. Table I shows than an equilibrium value of 50–55% of **2** resulted after ~0.5 hr in water or ~7 hr in methanol and was unchanged thereafter. The assumption that 55% of **2** is present at equilibrium results in $K \cong 6$.

TABLE I
FORMATION OF THE UNSYMMETRICAL DISULFIDE **2** BY EQUILIBRATION OF THE SYMMETRICAL DISULFIDES **3** AND **4** (61°)

| In $H_2O$ | | In MeOH | |
|---|---|---|---|
| Time, hr | Formation of **2**, % | Time, hr | Formation of **2**, % |
| 0.5[a] | ~50 | 0.5 | ~0 |
| 7 | ~55 | 7[a] | ~50 |
| 19 | ~50 | 19 | ~55 |
| 28 | ~55 | 28 | ~55 |

[a] Equilibration time first reached. At this time, the tlc spot for **2** had an area which did not increase significantly thereafter and which corresponded to a yield of ~50–55% for **2**.

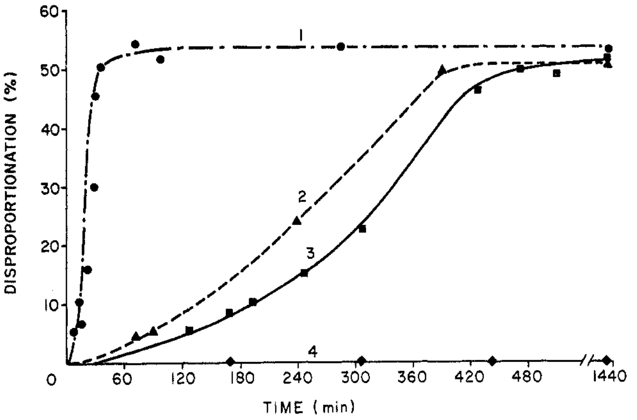

Figure 1.—Disproportionation of **2** under various conditions (61°): curve 1, ●, in $H_2O$; curve 2, ▲, in MeOH containing NaOMe equal to mol of **2**; curve 3, ■, in MeOH; curve 4, ◆, dry solid.

Comparison of the rapidity with which equilibrium was achieved under various circumstances was desirable in order to assess better the importance of $-SO_2^-$ in accelerating disproportionation. Fortunately, **2**, **3**, and **4** could be separated cleanly by tlc, and good calibration curves were possible by correlating spot areas with known amounts of **2**, **3**, and **4**. Since this method is not highly precise, it is appropriate to discuss results in terms of the more cautious word "rapidity" rather than of "rates." Nevertheless, use of the tlc correlations for analysis of test mixtures showed the results to be within about ±5% (this method was used in determining the data for Table I and Figure 1).

If disproportionation of **2** is in fact accelerated by a neighboring-group effect of $-SO_2^-$ on the disulfide linkage, the rapidity would be expected to be significantly greater for **2** than for **1**, the amide of **1** (**5**), or the sulfonate analog of **2** (**6**), since **1**, **5**, and **6** contain no $-SO_2^-$ moiety; solvent effects also might be anticipated with **2**, corresponding to variable tightness of ion pairs. The results of experiments that bear on these points are summarized in Figure 1 and Table II.

Further assurance as to the reliability of the conclusions from tlc was provided by a check isolation of **3** from the disproportionation of **2** at a point where the results indicated equilibrium had been reached; the two results agreed well (50% of **3** isolated after 8 hr for **2** in methanol; curve 3 of Figure 1 predicts 50%).

When the relative rapidity of the disproportionation of **2** in water and methanol are compared, disproportionation in water is seen to be about 21 times faster from Table II and clearly more rapid from Figure 1 (curve 1 *vs.* curve 3). It seems likely that $-SO_2Na$ is a much tighter ion pair in methanol than in water, so that $-SO_2^-$ is less able to assist cleavage of the S–S bond. The fact that the rapidity of disproportionation was negligibly affected by a tenfold increase in concentration seems more consistent with an intra- than an intermolecular effect (Table II, 0.4 *vs.* 0.5 hr). There is little increase of rapidity in going from methanol to a methanol–methoxide mixture (curve 2, Figure 1; relative rapidity of ~1.4 from Table II). Hence the possibility that the $-SO_2^-$ functions significantly as a weak base can be disregarded, and the slight acceleration seen can be attributed to attack of methoxide ion on the -SS- bond (or on a proton $\alpha$ to it) to generate

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[3] L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972).

[4] (a) For leading references, see ref 4b; (b) L. Field, W. S. Hanley, and I. McVeigh, *J. Org. Chem.*, **36**, 2735 (1971).

[5] For leading references, see L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966), especially footnote 7.

[6] H. Haraldson, C. J. Olander, S. Sunner, and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960).

TABLE II

DISPROPORTIONATIONS OF UNSYMMETRICAL DISULFIDES 1, 2, 5, AND 6 AT 61°

| Compd | Solvent | Time of reaction, hr | Disproportionation, % | $k_{\text{approx}}$,[a] sec$^{-1}$ | Relative rapidity |
|---|---|---|---|---|---|
| **2** | MeOH | 8[b] | ~50[b] | $1.5 \times 10^{-5}$ [b] | 1 |
| **2** | $H_2O$ | 0.5[c] | ~50–55[c] | $3.1 \times 10^{-4}$ [c] | 21 |
| **2** | $H_2O$ | ~0.4[d] | ~55[d] | | |
| **2** | MeOH–NaOMe | 6.5[e] | ~50[e] | $2.1 \times 10^{-5}$ | 1.4 |
| **2** | None | 72[f] | Trace | | |
| **1** | MeOH | 8 | 0 | | |
| **1** | $H_2O$[g] | 72[g] | 79[g] | | *h* |
| **1** | $H_2O$ | 8 | Trace | | |
| **5** | MeOH | 8 | 0 | | |
| **6** | $H_2O$ | 1.5 | 0 | | |
| **6** | $H_2O$ | 96 | Trace | | |

[a] Apparently first order, as seen with several other disproportionations (*cf.* ref 9, especially footnotes 6 and 7). [b] *Cf.* Figure 1, curve 3. [c] *Cf.* Figure 1, curve 1. [d] The concentration of **2** was ten times that for Figure 1, curve 1; ~0.4 and 0.5 are considered essentially the same, within experimental error, but because small amounts of **2** had to be used, calculation of $k_{\text{approx}}$ was not justified. [e] *Cf.* Figure 1, curve 2. The reaction was done as it was in MeOH but with a molar amount present of NaOMe equal to that of **2**. [f] *Cf.* Figure 1, curve 4. [g] Done at 100° (see ref 2). [h] Relative rapidity unknown but clearly *much* less than for **2**.

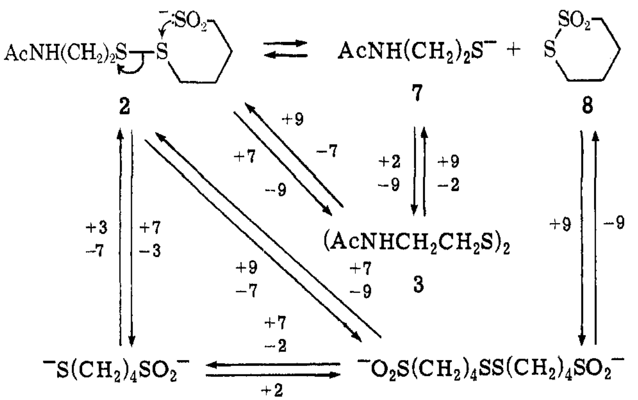
thiolate ion as a catalyst. The sulfinate **2** resists disproportionation as a solid. When it was heated dry at 61° for 25 hr it was stable; even after 72 hr, tlc indicated only slight disproportionation. The results of Table II are *highly* significant in that **1**, **5**, and **6**, which contain no $-SO_2^-$ moiety but otherwise are close counterparts of **2**, are stable under conditions that result in disproportionation of **2** (*cf.* eq 2 *vs.* eq 1).[7]

$$2X(CH_2)_2SS(CH_2)_4Y \xrightarrow{\text{very slow}} [X(CH_2)_2S]_2 + [S(CH_2)_4Y]_2 \quad (2)$$

**1**, $X = H_3N^+Cl^-$; $Y = SO_2CH_2Ph$
**5**, $X = AcNH$; $Y = SO_2CH_2Ph$
**6**, $X = AcNH$; $Y = SO_3Na$

The facts above thus support the probability that the disproportionation of **2** is initiated by a neighboring-group attack of $-SO_2^-$ on the –SS– bond, probably with 2-acetamidoethanethiolate ion (**7**) as a leaving group, as shown in Scheme I. Thiolate ion **7** then could catalyze the disproportionation of **2**.[8a] Scheme I illustrates reactions in which the thiolate **7** and 1,2-dithiane 1,1-dioxide (**8**) could be engendered and in which the other possible sulfinate ion **9** then could be formed to serve as a catalyst like **7**. Such equilibria could lead to the mixture of **2**, **3**, and **4** summarized at the outset by eq 1. Scheme I has much in common with similar ones that are believed to involve neighboring-group effects of amino[8b] or *o*-carboxylate moieties,[9] although the earlier ones were less complex since they went essentially to completion and could not be significantly reversed.

SCHEME I



It was possible in the *o*-carboxylate series to show that a cyclic intermediate like **8** was feasible.[9] It was satisfying to be able to confirm neighboring-group attack directly in the present instance by isolating the stable dioxide **8** (39% yield) after heating an aqueous solution of **2** in the presence of *N*-ethylmaleimide as a trap for the thiolate **7** and of benzene to remove the dioxide **8** from the sphere of the reaction. The isolation of **8** has the further important implication that $-SO_2^-$ exerts its effect through the proposed *intra*- rather than an *inter*molecular attack, since formation of **8** in the presence of a thiol trap is hard to envision by an intermolecular process.

One wonders whether the ambident $-SO_2^-$ ion exerts its effect by attack of an unshared pair of electrons of the oxygen atom, or of the sulfur atom as in Scheme I. The formation of the dioxide **8** strongly supports the view of attack by an electron pair of the sulfur atom; so, too, does failure of the sulfonate **6** to disproportionate nearly so readily as the sulfinate **2**. Also consistent is the finding of Meek and Fowler that the ambident sulfinate ion gives sulfones (*cf.* **8**) with "soft" alkylating agents (*cf.* the soft sulfur atom at which attack is suggested in Scheme I) but sulfinate esters preferentially with "hard" alkylating agents.[10] It should be noted that neighboring-group participation by sulfinyl oxygen in solvolysis of chloroalkyl sulfoxides greatly exceeds any such effect by sulfides (or

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(7) When the amino sulfone hydrochloride **1** was heated at 61° in methanol for 8 hr, **1** was quantitatively recovered. Since disproportionation of **1** at 100° in water for 72 hr gave one of the symmetrical disulfides in 79% yield,[2] however, disproportionation of **1** *can* occur. When **5** was heated at 61° in MeOH for 8 hr, it was recovered quantitatively, and in water (same conditions) only a trace of one of the symmetrical disulfides was obtained. The aqueous solution of **6** after 1.5 hr at 61° showed only the one spot for recovered **6** ($R_f$ 0 on alumina, 0.69 on silica gel) with none whatever for **3** ($R_f$ 0.45 on alumina); evaporation gave pure **6**; even after 96 hr at 61°, tlc showed only slight traces of disproportionation (small spot for **3** on alumina). Identifications of recovered **1**, **5**, and **6** were performed by comparing ir absorptions and melting points.

(8) (a) For further discussion of the catalytic effect of thiolate ion on disproportionation, see ref 8b; (b) M. Bellas, D. L. Tuleen, and L. Field, *J. Org. Chem.*, **32**, 2591 (1967).

(9) L. Field, P. M. Giles, Jr., and D. L. Tuleen, *J. Org. Chem.*, **36**, 623 (1971).

(10) J. S. Meek and J. S. Fowler, *ibid.*, **33**, 3422 (1968).

sulfones),[11a] and that it can be involved also in other reactions at electrophilic carbon atoms.[11b] However, this difference of the functioning of oxygen rather than sulfur is not surprising, since a carbon center should be much harder than a sulfur center (solvation also may be a factor; *cf.* ref 11a). The six-membered ring of **8** no doubt favors lone-pair participation of sulfur in **2**, however, so that in homologs of **2** lone-pair participation of oxygen conceivably might become important.

In summary, the main points that support neighboring-group assistance of $-SO_2^-$ to disproportionation are these. (1) The $-SO_2^-$ moiety is far more effective than $-SO_2R$ or $-SO_3^-$. (2) Reaction is faster in water than in methanol, and the reaction seems to be first order. (3) A tenfold increase in concentration had little effect on the rapidity of disproportionation. (4) **8** was isolated.

It was of considerable interest to compare neighboring-group participation of carboxylate ion with that of sulfinate (carboxylate groups were the first used in studying neighboring-group participation).[12] Two other features of carboxylates also were attractive. (1) For a study of variable effects in homologs, $RSS(CH_2)_nX$, synthesis promised to be easier with $X = CO_2^-$ than with $X = SO_2^-$ (a study of homologs with $R = Ac$ and $X = CO_2^-$ failed because of the lability of Ac to agents used to convert the carboxylic acids to the salts).[4b] (2) Although **2** is a promising antiradiation drug,[2,3] quite possibly because of the anchimeric effect of $-SO_2^-$, its ease of disproportionation in solution and its redox properties might present problems in its practical use. Carboxylates offered a prospective compromise in ease of handling and stability with neighboring-group induced activity as antiradiation drugs.

Three methods to prepare **12** were examined. Only from the reaction of the thiolsulfonate **10** with 3-mercaptopropionic acid in alkaline media could **12** be obtained successfully in good yield (eq 3). The method

$$\underset{\mathbf{10}}{AcNH(CH_2)_2SSO_2(CH_2)_2NHAc} + HS(CH_2)_nCO_2H \xrightarrow{NaOH,\ 0\text{–}10^\circ}$$

$$AcNH(CH_2)_2SS(CH_2)_nCO_2H + AcNH(CH_2)_2SO_2Na \quad (3)$$

$$\begin{array}{ll} \mathbf{11}, n = 1 & \mathbf{13}, n = 3 \\ \mathbf{12}, n = 2 & \mathbf{14}, n = 4 \end{array}$$

of eq 3 then was used also to prepare the homologs **11**, **13**, and **14**. The buffering action of the carboxylate ion doubtless led to sufficient thiolate ion to provide a rapid reaction. (2-Acetamido)ethanesulfinic acid, the strongest acid species present, formed as the salt (presumably), leaving **11–14** as extractable free acids (yields, 77–97%). Nmr, ir, and mass spectra and elemental analyses met expectation. The activity of **11–14** as antiradiation drugs proved to be minimal ($ALD_{50}$ ~175–480 mg/kg; 13–27% survival 30 days after irradiation of mice dosed with ~$^1/_2$ the $ALD_{50}$).[13]

The reaction of diethyl azodicarboxylate with two different thiols,[14] as appropriate for **11** and **12**, was unsuccessful; the main products were the symmetrical disulfides. An effort also failed to prepare **11** by conversion of either thiol to its sulfenyl chloride at −20°, for reaction with the other thiol; only polymers were obtained.

The acids **11–14** resisted disproportionation at 61° in methanol or water. Tlc showed no change after 3 days, and no acetamidoethyl disulfide (**3**) was detected in confirming experiments; each acid also was isolated quantitatively after 3 days.

On the other hand, the salts of the acids disproportionated fairly readily in water. Similar observations were made for 2-(phenyldithio)benzoic acid (**15**) and its salt **15′**; the more rapid disproportionation of **15′** was attributed to anchimeric assistance by the ortho $CO_2^-$ moiety in a scheme resembling Scheme I.[9] Such observations are not surprising, since "when the carboxylate group is converted by protonation to the carboxyl group, –COOH, it becomes very much less nucleophilic and loses a great deal of its effectiveness as a participant."[12]

As with **2**, disproportionation of **11–14** as the salts (**11′–14′**; from **11–14** using NaOH at pH ~7–8) gave the symmetrical disulfide **3**. The yields of **3** isolated appear to represent near-equilibrium values, since Table III shows that disproportionation of **13′** and **14′** reached values of ~44% in ~2–3 hr at latest and then remained constant. Since the disproportionation thus appears to be reversible, the equilibria of eq 4 seem to be the best way to represent the reactions.

Table III

Equilibrium in the Disproportionation of Salts **13′** and **14′**

| | Time, hr[a] | | | | |
|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 9 |
| **13′**, disproportionation, % | 37 | 41 | 45 | 43 | 44 |
| **14′**, disproportionation, % | 38 | 44 | 42 | 43 | 46 |

[a] Determined after heating **13** or **14** in the presence of ~1 equiv of NaOH in $H_2O$ (pH 8) at 61° and isolating **3** (see Experimental Section).

$$2AcNH(CH_2)_2SS(CH_2)_nCO_2H \overset{2NaOH}{\rightleftarrows}$$

$$\begin{array}{ll} \mathbf{11}, n = 1 & \mathbf{13}, n = 3 \\ \mathbf{12}, n = 2 & \mathbf{14}, n = 4 \end{array}$$

$$\underset{\mathbf{11'}\text{–}\mathbf{14'}}{2AcNH(CH_2)_2SS(CH_2)_nCO_2Na} + 2H_2O \quad (4)$$

$$\downarrow\uparrow$$

$$\underset{\mathbf{3}}{[AcNH(CH_2)_2S]_2} + [S(CH_2)_nCO_2Na]_2$$

The fact that both **13′** and **14′** required about the same length of time to reach equilibrium (Tables III and IV), even though the presumed anchimeric effect of oxygen on the nearest sulfur atom would involve a six- and a (less favorable) seven-membered ring, respectively, is surprising; this similarity may even argue against an anchimeric effect as the sole accelerating factor. Perhaps this apparent similarity in reactions has its basis in simultaneous involvement of direct attack of hydroxyl ion on the –SS– bond or of subtle

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[11] (a) M. Cinquini, S. Colonna, and F. Montanari, *Tetrahedron Lett.*, 3181 (1966); (b) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. C*, 572 (1970).

[12] For a review, see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston, New York, N. Y., 1959, p 561 ff.

[13] For details on methods, see ref 3. We are indebted for these results to T. R. Sweeney, D. L. Klayman, and (especially) M. M. Grenan of the Walter Reed Army Institute of Research, Washington, D. C.

[14] T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968).

TABLE IV

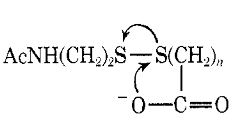
DISPROPORTIONATION OF **11–14** AND OF **11′–14′** IN $H_2O$

| Expt | Compd | Base | Molar ratio, compd:base | pH | Temp, °C | Time to equilibrium point, min[a] |
|---|---|---|---|---|---|---|
| 1 | **11** | | | 2.5 | 61 | Slow[b] |
| 2 | **12, 13, 14** | | | 3.2, 3.5, 3.5 | 61 | Very slow[c] |
| 3 | **11** | NaOH | 1:1.04 | 8 | 25 | Very fast[d] |
| 4 | **12, 13, 14** | NaOH | 1:1.04 | 8 | 40 | 110 |
| 5 | **12, 13, 14** | NaOH | 1:1.04 | 8 | 61 | 10 |
| 6 | **14** | NaOH | 1:2 | ~13 | 40 | 5[e] |
| 7 | **2** | | | 6.8 | 40 | 90 |
| 8 | **14′** | $NEt_3$ | 1:2 | ~12 | 40 | 240[e] |
| 9 | **11′** | | | 6.6 | 61 | ~465 |
| 10 | **12′** | | | 6.6 | 61 | ~7200 |
| 11 | **13′** | | | 6.8 | 61 | ~8600 |
| 12 | **14′** | | | 6.8 | 61 | ~8880 |
| 13 | **2** | | | 6.8 | 61 | 30 |

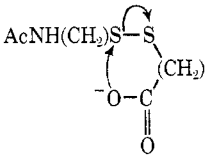
[a] *I.e.*, the time at which the tlc spot area of **3** became constant. [b] Began to disproportionate after 4 days. [c] Began to disproportionate after 16 days. [d] Compound 11 disproportionated immediately at pH 8 at 25°. [e] At these high values of pH, direct attack of $OH^-$ on $-SS-$ or $-CH_2S-$ is probable.

changes in amounts of catalytic thiolate species as a function of pH.

For further studies, the salts **11′–14′** were prepared by precipitation from methanol. Tlc analyses for **3** could be used to follow their reactions and those of **11–14** approximately, much as with **2**. Table IV shows times required for attainment of equilibrium of **11–14** and **11′–14′** under various conditions. There are three notable points. (1) As was the case with 2-(phenyldithio)benzoic acid (**15**),[9] the rapidity of disproportionation is highly sensitive to pH (*cf.* expt 1 *vs.* 3 and 2 *vs.* 5, 6). (2) The salt with $n = 1$ (**11′**) disproportionates far more rapidly than those with $n = 2$-4 (**12′–14′**); *cf.* expt 3 *vs.* 5 and 9 *vs.* 10, 11, and 12); compounds **12′–14′** seem roughly comparable (*cf.* expt 4 or 5 and also 10–12). Analogy with Scheme I suggests involvement of **16a** for participation of $-CO_2^-$ in disproportionation.[15]



**16a**



**16b**

There is little basis at present for speculation, however, as to why **11′** disproportionates so much more rapidly than **12′–14′** or why **12′–14′** are comparable. It may be that, in generation of thiolate ion catalyst from **11′**, a four-membered ring (**16a**, $n = 1$) is unexpectedly effective, or that **16b** becomes important, or that the greater acidity of the methylene group in **11′** (flanked both by $-S-$ and $-CO_2^-$) leads to loss of $AcNH(CH_2)_2S^-$ by $\alpha$ elimination. (3) The sulfinate **2** disproportionates faster than the comparable carboxylate **14′** by a factor of ~300 (*cf.* expt 12 *vs.* 13).

Although a neighboring-group effect seems much more clear-cut for $-SO_2^-$ than for $-CO_2^-$, points that support neighboring-group acceleration by $-CO_2^-$ can be summarized as follows. (a) Although the free acids **11–14** strongly resist disproportionation, the salts do not. (b) The rapidity of disproportionation is highly dependent on pH near the neutral point, presumably increasing as the amount of $-CO_2^-$ increases. (c) Variation of the distance separating the carboxylate and disulfide functions has a marked effect, even though its meaning is not clear at present.

Overall, the general conclusions seem justified that neighboring-group effects of both 4-sulfinate and $\omega$-carboxylate moieties accelerate disproportionation of disulfides, although the effect with carboxylate is considerably more speculative, less effective, and more complex in its interaction.

## Experimental Section[16]

**Materials.**—Compounds **2**,[3] **3**,[17] **4**,[3] **8**,[18] **10**,[19] and 2-acetamidoethanethiol[20] were prepared using the procedures cited. The aminosulfone **1**, the acetamidosulfone **5**, and the acetamidosulfonate **6** were available from the work of Barbee.[2] Commercial mercaptoacetic acid ($H_2O$ solution, dried to an oil at 0.1 mm), 3-mercaptopropionic acid, and 4-mercaptobutyric acid (Distillation Products Industries) were used after checking them by ir and nmr. All other materials were commercial products used as received.

**Disproportionation of Sodium 4-(Acetamidoethyldithio)butanesulfinate (2). A. Isolation of 2-Acetamidoethyl Disulfide (3) and Disodium 4,4′-Dithiobis(butanesulfinate) (4).**—Details were reported earlier for isolation of **3** and **4**.[3] Briefly, after **2** has been heated in MeOH (8 hr, 61°), evaporation and extraction gave **3** in 50% yield, which was characterized by melting point and ir. A similarly heated methanolic solution was treated with $Me_2CO$ to precipitate **2** and **4**; the precipitate then was reheated in MeOH and reprecipitation was carried out until **4** resulted that contained only a trace of **2** by ir or tlc and no **3**; the yield of **4** was 42%, and analyses were satisfactory (C, H, Na, S). This analytically pure **4** was used for the tlc calibration curves described in section C.

**B. Reversibility of Eq 1.**—Solutions of **3** (4.00 mg, 0.017 mmol) and **4** (6.0 mg, 0.017 mmol) in 1 ml each of $H_2O$ and MeOH

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[15] A five-membered ring evidently is involved in anchimerically assisted racemization of sulfoxides that contain $-CO_2H$ moieties. See S. Allenmark and C.-E. Hagberg, *Acta Chem. Scand.*, **24**, 2225 (1970), and earlier papers.

[16] Melting points are corrected, and boiling points are uncorrected. Nmr spectra were obtained with a Varian Model A-60 and ir spectra with a Beckman Model IR-10 using KBr pellets or NaCl plates (bands reported are at least of medium intensity). Moist extracts were dried over the anhydrous agent specified; solvent then was evaporated in a rotary evaporator. Brinkmann precoated tlc sheets of silica gel (F-254, 0.25 mm) and Eastman Chromagram sheets of alumina (Type 6063 with fluorescent indicator) were used for tlc; with the former, spots were observed after exposure to $I_2$ vapor in a sealed container, and with the latter, spots were observed under a uv lamp. Other details were essentially as given in footnote 13 of ref 1a.

[17] L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

[18] L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969).

[19] J. D. Buckman and L. Field, *ibid.*, **32**, 454 (1967).

[20] R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

were heated at 61° in a constant-temperature oil bath. From time to time, 10 μl of the solution was withdrawn and spotted on a silica-gel layer. The amount of **2** present was obtained by tlc as described in section C. The results are shown in Table I.

**C. Rapidity of Disproportionation.**—Tlc on silica gel[16] with 1:2 MeOH–$Me_2CO$ was used to separate **2** ($R_f$ 0.66), **3** ($R_f$ 0.84), and **4** ($R_f$ 0.33); the starting point for spots was 2.5 cm from the bottom of the tlc plate and the final solvent front was ~12 cm. Calibration curves for semiquantitative analysis were obtained by measuring the spot areas (by counting squares on a spot of equivalent size on graph paper) of **2**, **3**, and **4**, corresponding to known weights, using usual methods;[21] in constructing the curve, five mixtures of **2**, **3**, and **4** were used in which the respective amounts and proportions were varied; for example, a solution (30% disproportionation supposed) containing **2** (21.0 mg), **3** (3.6 mg), and **4** (5.4 mg) was spotted on three silica-gel plates as described above and then areas of the spots of **2** and **4** were measured and the average value was calculated. In such chromatography the square root of the spot area ($A$) is proportional to the logarithm of the amount of substances ($W$), so that $\sqrt{A} = m \log W + c$.[21] Hence a graph prepared by plotting $\sqrt{A}$ as a function of log $W$ (using 1.8–9.0 mg of **4** in solution) could be used to estimate the amount present of **4**, and similarly for **2**; $m$ and $c$, constants, were 0.40 and 0.67, respectively. This method gave, for example, the amounts of **4** in mixtures of **2**, **3**, and **4** within about ±5% as evidenced by comparisons of percentages of **4** in prepared mixtures with percentages found (in parentheses): 10 (8, 12), 20 (18, 15), 30 (26, 35), 40 (37, 43), 50 (56).

In a typical experiment on the rapidity of disproportionation of **2** to give **3** and **4**, a solution of **2** (30 mg, 0.102 mmol) in MeOH (5 ml) was heated at 60.8 ± 0.2° in a constant-temperature oil bath. From time to time 10 μl of the reaction solution was withdrawn using a microsyringe and was spotted on a silica gel layer. Comparison of the spot areas of **4** with those of the calibration curves gave the amounts of **4**. All of the reactions summarized in Figure 1 and Table II were done under essentially the same conditions, and no solid was present in any of the solutions. Values of $k_{approx}$ (Table II) were calculated by converting the mass of **4** from the tlc plot to moles, considering $C_0$ based on 0.102 mmol, subtracting twice the moles of **4** at time $t$ from 0.102 to get $C$, plotting log $(0.102/C)$ *vs.* $t$ (min), taking the slope, and multiplying by 2.303. The disproportionation per cent (Table II and Figure 1) was calculated as (100)(2)·(mmoles of **4**)/(0.102).

**D. Isolation of 1,2-Dithiane 1,1-Dioxide (8).**—*N*-Ethylmaleimide (0.214 g, 1.71 mmol) was added slowly to a mixture of $H_2O$ (10 ml) and benzene (15 ml) containing **2** (0.500 g, 1.71 mmol) at 0°. After the reaction mixture had been heated at 60° for 50 min with good stirring, the $H_2O$ layer was separated and was washed with benzene. The combined benzene layers were washed with $H_2O$, dried ($Na_2SO_4$), and concentrated. The crude **8** obtained (0.100 g, 39%) had mp 45–49°. Recrystallization from $Et_2O$–hexane gave **8**, mp and mmp 52–53° (lit.[18] mp 54.5–55°), which had an ir spectrum identical with that of authentic **8**.[18]

**(2-Acetamidoethyldithio)ethanoic Acid (11).**—A solution of NaOH (4.21 g, 0.105 mol) in $H_2O$ (15 ml) was added slowly (~0.5 hr) to mercaptoacetic acid (9.65 g, 0.105 mol) in MeOH (40 ml) at 0°. The resulting solution was kept at 0° and was added (~2 hr) to **10** (26.8 g, 0.100 mol) in MeOH (100 ml) at ~0° with good stirring during ~2 hr. Tlc then showed no spot on alumina corresponding to **10**. The solution was carefully concentrated to about 40 ml at 25° (rotary evaporator, condenser at 0°), saturated with NaCl, and extracted with several 150-ml portions of $CHCl_3$. The extract, dried ($MgSO_4$) and concentrated at ~25°, gave 17.0 g (81%) of white **11**, mp 85–88°. Recrystallization by dissolution in $Me_2CO$ at ~25°, addition of $Et_2O$ to incipient turbidity, and chilling gave **11** as white crystals of constant mp 92–93°: nmr ($CDCl_3$) δ 2.03 (s, $CH_3CO$), 5.81 ($CO_2H$); ir 3360, 1690, 1570, 1540, 1300, 1190, 1175, and 890 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 43 (100), 60 (65), 86 (90), 118 (50), 151 (5), 186 (4), 209 (1).

*Anal.* Calcd for $C_6H_{11}NO_3S_2$: C, 34.41; H, 5.27; N, 6.70; S, 30.62; mol wt, 209. Found: C, 34.42; H, 5.34; N, 6.79; S, 30.84; mol wt, 209 (mass spectrum).

**3-(2-Acetamidoethyldithio)propanoic Acid (12).**—Aqueous NaOH solution (3.76 g, 93.3 mmol in 100 ml of $H_2O$) was added slowly (40 min) to a mixture of **10** (25.0 g, 93.30 mmol) and 3-mercaptopropionic acid (9.90 g, 93.30 mmol) in 200 ml of $H_2O$ at 0–5° with stirring; solid began to appear at once. The mixture was kept at 25° for 1 hr and then was chilled (0°); filtration gave 13.0 g of white **12**. The mother liquor, extracted with $CHCl_3$, gave 3.0 g of **12**. Accordingly, 16.0 g (77%) of **12** was obtained, mp 80–83°. Recrystallization as with **11** gave **12** as white plates of constant mp 85–86°: nmr ($CDCl_3$) δ 2.03 (s, $CH_3CO$), 9.60 (s, $CO_2H$); ir (KBr) 3340, 1705, 1615, 1560, 1540, 1330, 1240, 1185, 900 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 43 (100), 60 (30), 86 (95), 118 (22), 164 (9), 210 (3), 223 (1).

*Anal.* Calcd for $C_7H_{13}NO_3S_2$: C, 37.68; H, 5.83; N, 6.28; S, 28.69; mol wt, 223. Found: C, 37.88; H, 6.01; N, 6.16; S, 28.48; mol wt, 223 (mass spectrum).

**4-(2-Acetamidoethyldithio)butanoic Acid (13).**—As with **12**, NaOH (2.8 g, 70.0 mmol) in $H_2O$ (50 ml) was added in part to **10** (20.0 g, 74.5 mmol) and 4-mercaptobutanoic acid (8.40 g, 70.0 mmol) at 0–5° with stirring. Immediate precipitation made stirring difficult. Water (200 ml) was added, and addition of NaOH was continued. The mixture was let stand at ~25° for 2 hr. Treatment as for **12** gave 15.0 g (90%) of white **13**, mp 82–85°. Recrystallization as with **11** gave **13** of constant mp 87–88°: nmr ($CDCl_3$) δ 2.03 (s, $CH_3CO$), 17.1 (s, $CO_2H$); ir (KBr) 3330, 1715, 1635, 1585, 1300, 1220, 1180 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 43 (100), 60 (15), 86 (80), 118 (14), 151 (12), 178 (2), 237 (1).

*Anal.* Calcd for $C_8H_{15}NO_3S_2$: C, 40.55; H, 6.34; N, 5.91; S, 27.00; mol wt, 237. Found: C, 40.31; H, 6.19; N, 5.80; S, 26.91; mol wt, 237 (mass spectrum).

**5-(2-Acetamidoethyldithio)pentanoic Acid (14).**—**5-Mercaptopentanoic acid** was synthesized as follows.[22] A mixture of δ-valerolactone (100 g, 1.19 mol) and thiourea (83.6 g, 1.10 mol) in 48% HBr (1.2 mol) was heated under reflux for 10 hr. The mixture then was made strongly basic with 50% aqueous NaOH until a homogeneous solution resulted, which was heated under reflux for 2.5 hr and then was allowed to stand overnight. The solution was acidified with $H_2SO_4$, and an $Et_2O$ extract was washed with $H_2O$, dried ($MgSO_4$), and concentrated. Distillation gave 85.0 g (58%) of 5-mercaptopentanoic acid: bp 103–105° (0.7 mm); nmr ($CDCl_3$) δ 1.27 (t, SH), 12.06 (s, $CO_2H$); ir 2940, 2660, 2580, 2320, 1715, 1420, 1285, 1230 $cm^{-1}$.

Much as with **12**, NaOH (2.80 g, 70.0 mmol) in 50 ml of $H_2O$ then was added to **10** (20.0 g, 74.5 mmol) and 5-mercaptopentanoic acid (9.40 g, 70.0 mmol) in 100 ml of $H_2O$ at 5–10°, giving 17.0 g (97%) of **14**, mp 60–65°. Recrystallization as with **11** gave **14** of constant mp 69–70°; nmr δ 2.03 (s, $CH_3CO$), 9.67 (s, $-CO_2H$); ir (KBr) 3370, 2955, 2880, 1715, 1630, 1560, 1425, 1285, 1210, 1185 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 43 (100), 60 (17), 86 (90), 118 (14), 192 (1), 251 (2).

*Anal.* Calcd for $C_9H_{17}NO_3S_2$: C, 43.10; H, 6.78; N, 5.58; S, 25.58; mol wt, 251. Found: C, 42.90; H, 6.60; N, 5.42; S, 25.52; mol wt, 251 (mass spectrum).

**Disproportionation of the Acids 11–14 and Their Salts 11′–14′. A. Of 11–14.**—In a typical experiment, a solution of **12** (111.5 mg, 0.05 mmol) in 5 ml each of MeOH in $H_2O$ was heated at 61°. From time to time 10 μl of the solution was withdrawn by a microsyringe and spotted on an alumina layer (solvent, 1:2 benzene–$Me_2CO$). After 3 days of heating, tlc showed no spot of **3** ($R_f$ of **3**, 0.45; of **11–14**, 0).[23]

When **12** (45 mg, 0.2 mmol) in MeOH (10 ml) was heated at 61° for 3 days, 44 mg (98%) was recovered (identity was assured by melting point and ir). After 3 days, **11**, **13**, and **14** were stable in both $H_2O$ and MeOH at 61°; **11**, **13**, and **14** were each recovered (~100% from MeOH).

**B. Isolation of 3 after Heating of 11′–14′.**—Illustratively, aqueous NaOH (82.0 mg, 2.04 mmol) was added to **12** (446 mg, 2.00 mmol) in $H_2O$ (25 ml); the pH then was ~8. The solution was heated at 55–60° for 13 hr and then was extracted with $CHCl_3$ three times. The extract was washed with cold $H_2O$, dried ($MgSO_4$), and concentrated: yield of **3**, 85.0 mg (36%); ir spectrum identical with that of authentic **3**; mp 91–92° (lit.[17]

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[21] K. Randerath, "Thin-Layer Chromatography," 2nd ed, Academic Press, New York, N. Y., 1966, p 70 ff.

[22] Based on the procedure of Kodak Society, Belgian Patent No. 593,048 (1960); *Chem. Abstr.*, **55**, 14142 (1961).

[23] Eastman Chromagram sheet Type 6063 alumina with fluorescent indicator; uv was used in searching for **3**.

mp 92–93°). The values for disproportionation per cent of 37–46% mentioned for **13** and **14** (see discussion) were obtained similarly.

C. **Equilibration of 13′ and 14′.**—*A solution of the acid* **13** (1.04 g, 4.39 mmol) in $H_2O$ (50 ml) containing NaOH (0.176 g, 4.40 mmol) was heated at 61° (pH ~8). From time to time, 10 ml was withdrawn, saturated with NaCl, and extracted with $CHCl_3$. Removal of $CHCl_3$ gave **3**, which was recrystallized from $Me_2CO$-$Et_2O$ and then identified by ir and melting point. Compound **14** was treated similarly, and disproportionation per cent was calculated as described above (previous section C). The results based on the weight of **3** isolated are shown in Table III.

D. **Disproportionation of Salts 11′–14′.**—For the preparation of the sodium salts **11′–14′** of the acids **11–14**, illustratively, a solution of NaOMe in MeOH (2.2 ml of 1.0 *N*) was added to **14** (0.55 g, 2.2 mmol) in MeOH (3 ml) to a pH of 6.8–7.0. Addition of dry $Me_2CO$ then immediately precipitated white **14′**. Decantation and drying at 0.1 mm gave **14**, which was washed with acetone and then was dried again at 0.1 mm under vacuum, mp 188° dec. Compounds **11′**, **12′**, and **13′** were obtained similarly, except that with **11′** and **12′** dry $Et_2O$ was used instead of $Me_2CO$ because **11′** and **12′** are slightly soluble in $Me_2CO$. *Melting points follow:* **11′**, 280° dec; **12′**, 120–122°; and **13′**, 215° dec. The purity of **11′–14′** was confirmed by checking absence of any **3** by tlc on alumina.

The disproportionation results of Table IV were obtained using ~1 mmol in 10 ml of $H_2O$ of **11′–14′** (or **11–14** where specified). Illustratively, a solution of **14′** (273 mg, 1 mmol) in 10 ml of $H_2O$ was heated at 61 ± 0.5° in a constant-temperature bath. From time to time, 5 μl was withdrawn by a microsyringe and spotted for tlc on an alumina layer.[23] The spot for disulfide **3** then was observed, and the time was reported in Table IV at which the area no longer increased.

**Registry No.**—**2**, 34915-80-5; **3**, 638-44-8; **4**, 34915-82-7; **11**, 34915-83-8; **11′**, 34915-84-9; **12**, 34915-85-0; **12′**, 34915-86-1; **13**, 34915-87-2; **13′**, 34915-88-3; **14**, 34915-89-4; **14′**, 34915-90-7.

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# Electron-Accepting Through-Conjugation Effects in Organosulfur Compounds

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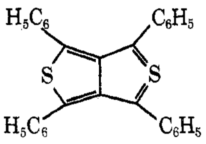
The importance of cyclic conjugation involving (p → d)-π bonding has been investigated in attempted syntheses of thianaphthalene derivatives and in the transmission of substituent effects through sulfur in *S*-phenacyl-*S*-phenyl-*S*-methylsulfonium salts as evaluated from $pK_a$ measurements. No evidence was obtained to support the concept of through-conjugation in the systems chosen for study.

There now exists a large body of experimental evidence regarding the electron-accepting properties of sulfur. These properties are generally described as valence-shell expansion by π bonding in which overlap occurs between a vacant 3d sulfur orbital and a filled 2p orbital of an adjacent first-row atom.[2] The importance, however, of 3d orbitals in supporting electron delocalization *through* sulfur remains a controversial issue. For example, the question of participation of 3d orbitals in the bonding of thiophene has been frequently discussed,[3] and it now appears that 3d and higher energy orbitals contribute very little to the bonding in thiophene in its ground state.[4] Positive evidence for through-conjugation by way of sulfur stems from the synthesis of stable sulfur heterocycles of the type **1**,[5] **2**,[6] **3**,[7] and **4**[8] in which sulfur may be viewed as quadricovalent in a delocalized π system. However, the stability of thiaaromatic compounds varies widely. For example, thiabenzenes **5**[7,9] and thianaphthalenes **3**[7] vary in stability according to the nature and position of substituents; the thiabenzene 1-oxide **6** is remarkably stable[9] although the chemical behavior of **6** more closely resembles that expected for an ylide structure than for a delocalized benzenoid structure. Likewise, the aromaticity of thiaphenalenes **2** is open to question,[3b] while thiepin dioxide **7** and related compounds, which are formally 6-π-electron systems related to tropone, do not appear to possess aromatic character.[10] The acidity of the cyclic sulfone **8** is unexceptional relative to that of the open-chain analog **9**, and this suggests that the carbanion derived from **8** lacks aromaticity.



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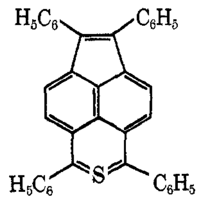

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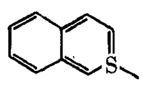

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While the experimental evidence is both positive and negative on the issue of through conjugation, theoretical arguments are not clear-cut either. Calculations illustrating the importance of cyclic conjugation

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[1] The authors wish to gratefully acknowledge the support received for this work from the National Science Foundation (GP 7278 and GP 12828).

[2] For reviews on the topic of sulfur bonding see (a) G. Cilento, *Chem. Rev.*, **60**, 147 (1960); (b) A. B. Burg in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, pp 30–40; (c) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962; (d) D. T. Clark in "Organic Compounds of Sulfur, Selenium, and Tellurium," Special Publication of the Chemical Society, D. H. Reid, Ed., London, 1970; (e) K. A. R. Mitchell, *Chem. Rev.*, **69**, 157 (1969).

[3] For recent reviews on valence-shell expansion in sulfur heterocycles, see (a) W. G. Salmond, *Quart. Rev., Chem. Soc.*, **22**, 253 (1968); (b) D. H. Reid in "Organic Compounds of Sulfur, Selenium and Tellurium," Vol. I, Special Publication of the Chemical Society, D. H. Reid, Ed., London, 1970.

[4] D. T. Clark, *Tetrahedron*, **24**, 2663 (1968); D. T. Clark and D. R. Armstrong, *Chem. Commun.*, 319 (1970); U. Gelius, B. Roos, and P. Siegbahn, *Chem. Phys. Lett.*, **4**, 471 (1970); M. J. S. Dewar and M. Trinajstić, *J. Amer. Chem. Soc.*, **92**, 1453 (1970).

[5] M. P. Cava and G. E. M. Husbands, *ibid.*, **91**, 3952 (1969).

[6] J. M. Hoffman, Jr., and R. H. Schlessinger, *ibid.*, **91**, 3953 (1969).

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[8] For a concise summary of the historical development of thiathiophenes, see ref 3a.

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