(55), 57 (100), 55 (71), 43 (79). *m*-Aminobenzonitrile (7.3%), mp 52–54°, mmp 52–54° (lit.[44] mp 53–54°), was also obtained.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.39; H, 5.68.

Kinetics of the Thermal Decomposition of *p*-Azidobenzonitrile in the Presence of *N,N*-Dimethylaniline.—*p*-Azidobenzonitrile was thermolyzed in chlorobenzene solution at 132° in the presence of varying amounts of *N,N*-dimethylaniline. During the thermolyses, portions were removed at regular intervals with a syringe, diluted fourfold with chlorobenzene, and assayed by measuring the area of the asymmetric azide stretching band in the infrared (2160 and 2110 cm^{-1}). Concentrations of azide were obtained from a previously prepared calibration curve,[45] and rate constants for the disappearance of azide were obtained from the slopes of plots of log [azide] *vs.* time. The results are summarized below.

[*p*-Cyanophenyl azide], *M*	[*N,N*-dimethylaniline], *M*	Rate constant ($\times 10^5$), sec^{-1}
0.02		1.47
0.02	0.02	1.47
0.02	0.06	1.70
0.02	0.10	1.48

(44) A. Fricke, *Ber.*, **7**, 1321 (1874).

(45) The variation of the area of this band with concentration deviated from linearity above 0.05 *M*, suggesting possible association of the azide in solution.

Registry No.—**2**, 18523-41-6; **3**, 29547-82-8; **4**, 29547-83-9; **7**, 34915-93-0; 2-(*N,N*-dimethylamino)-4′-trifluoromethyldiphenylamine, 29547-88-4; 4-(*N,N*-dimethylamino)-4′-trifluoromethyldiphenylamine, 34913-28-5; 4,4′-bis(trifluoromethyl)azobenzene, 34913-29-6; 4-cyano-2′,4′,6′-trimethoxydiphenylamine, 29547-84-0; 4-cyano-2′,4′,6′-trimethyldiphenylamine, 29547-85-1; 2-(*N,N*-dimethylamino)-4′-nitrodiphenylamine, 29547-86-2; 4-nitro-2′,4′,6′-trimethoxydiphenylamine, 29547-87-3; 4,4′-bis(trifluoromethyl)azoxybenzene, 34913-34-3; 2-cyano-2′,4′,6′-trimethoxydiphenylamine, 34913-35-4; 3-cyano-2′,4′,6′-trimethoxydiphenylamine, 34913-36-5.

Organic Disulfides and Related Substances. 34. Synthesis and Reactions of Some Substituted Cyclic Disulfides and Corresponding *S*-Oxides[1]

LAMAR FIELD* AND YONG H. KHIM

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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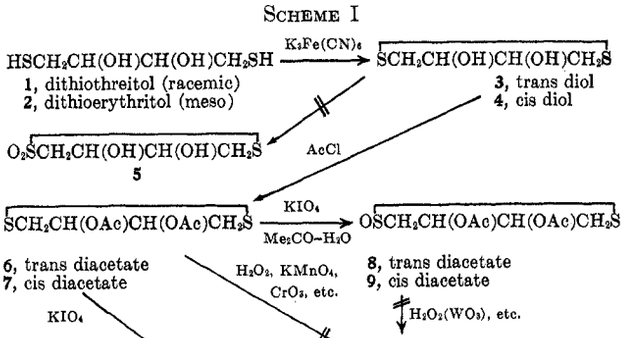
Functionally substituted 1,2-dithianes, 1,2-dithiolanes, and *S*-oxides were sought for study of their properties and reactions and for testing as antiradiation drugs. Oxidation of *trans*- and *cis*-1,2-dithiane-4,5-diol diacetate (**6** and **7**) gave the 1-monoxides **8** and **9**. Oxidation of **6** and **7** to the trans and cis 1,1-dioxides **10** and **11** failed with numerous agents but finally was accomplished using potassium metaperiodate in aqueous 2-propanol with iodine as an effective catalyst as the best means. A thiolate ion cleaved the 1,1-dioxide **10**, giving a disulfide sulfinate (**14**), but amines did not cleave 1,2-dithiane 1,1-dioxide (**12**). Procedures are compared for the synthesis of 1,2-dithiolane-4-carboxylic acid (**16**), and syntheses of some other dithiolanes are discussed.

This paper reports some syntheses and reactions of substituted five- and six-membered cyclic disulfides and of the corresponding *S*-oxides. There were two motivations for the work. One was to permit testing of representative compounds as antiradiation drugs, since *trans*-1,2-dithiane-4,5-diol (**3**) has been said to be active in this respect;[2] such activity would be of considerable interest because most antiradiation drugs contain nitrogen functions that may have much to do with their toxicity. A second motivation was to begin an extension to substituted systems of earlier studies of unsubstituted cyclic disulfides and their *S*-oxides.[3]

In Scheme I, conversion of dithiothreitol (**1**) to *trans*-1,2-dithiane-4,5-diol (**3**) and of dithioerythritol (**2**) to the cis isomer **4** proceeded by standard methods (70–75% yield); recrystallization provided a convenient purification. Although 1,2-dithiane can be oxidized to the 1,1-dioxide by hydrogen peroxide or potassium metaperiodate (KIO_4) in 66–68% yield,[3a] the dihydroxydithiane **3** gave only intractable oil with no indication of the dioxide **5** (ir); cleavage of **3** to sulfonic acids evidently predominated, since the products were strongly acidic, probably complicated by cleavage at the glycol moiety.

SCHEME I



It seemed likely that adverse reactions of the glycol moiety could be prevented by prior acetylation. Both of the diols **3** and **4** have been acetylated by means of acetic anhydride and pyridine but, since the diacetates **6** and **7** were desired for nmr studies, few other details were given.[4] Acetyl chloride gave the trans diacetate **6** and cis diacetate **7** in yields of 74–82% (Scheme I).

Oxidation of the diacetates **6** and **7** to the 1-monoxides **8** and **9** occurred, but oxidation to the 1,1-dioxides

(1) (a) Paper 33: L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (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. (c) We are indebted to Professor H. E. Smith of Vanderbilt University for helpful discussion.

(2) C. Falconi, P. Scotto, and P. De Francisois, *Boll. Soc. Ital. Biol. Sper.*, **44**, 326 (1968); *Chem. Abstr.*, **69**, 16658 (1968).

(3) (a) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969); (b) L. Field and R. B. Barbee, *ibid.*, **34**, 1792 (1969).

(4) A. Lüttringhaus, S. Kabuss, W. Maier, and H. Friebolin, *Z. Naturforsch. B*, **16**, 761 (1961).

10 and **11** proved far more difficult than had been anticipated from studies with 1,2-dithiane under similar or less vigorous conditions (*cf.* ref 3a). Thus with the trans diacetate **6**, hydrogen peroxide at 25° gave the monoxide **8** (64%), not the expected dioxide **10**, and longer times or higher temperatures led only to cleavage into presumed sulfonic acids (the pH dropped to 1–2). Similarly, a large excess of KIO_4 in aqueous acetone gave only **8** (85% yield). Other agents with **6** also gave only cleavage or monoxide **8**, with no indication through ir spectra of the dioxide **10**; these agents included potassium permanganate in acetone (38% of **8**), chromium trioxide in acetone (low yield of **8**), *m*-chloroperbenzoic acid, and ceric ammonium nitrate. The monoxide **8** itself was submitted to oxidation but was equally refractory. For example, under conditions that finally were made vigorous enough to destroy most of the **8** (*e.g.*, 5 days at 60°), aqueous KIO_4 led only to cleavage of **8**. Use of hydrogen peroxide–tungsten trioxide–sulfuric acid in dioxane–acetic acid, a combination useful for oxidizing another refractory disulfide to a dioxide,[5] also led mainly to cleavage (10% recovery of **8** after 48 hr at 25°, with no indication of **10**). With the cis diacetate **7**, fewer experiments were done because of the greater expense of **2** but, again, resistance to oxidation seemed marked. With KIO_4, the monoxide **9** was obtained in 80% yield from **7**, but various efforts to prepare the dioxide **11** were largely unavailing. On one occasion, KIO_4 in aqueous acetone did convert **7** to the dioxide **11** in 66% yield. The **11** thus could be characterized, but this preparation could not be repeated (see Experimental Section). The conditions required for the one successful preparation of **11** (40°, 50 hr), and particularly the failure of other efforts, seem to contrast sufficiently with those for oxidation of 1,2-dithiane to the dioxide (~25°, 4 days)[3a] to suggest that the cis diacetate **7** parallels the trans diacetate **6** in intransigence.

It is noteworthy that neither the monoxide **8** nor **9** seems to be particularly unstable (the melting point of **8** was unchanged after 20 months). In stability **8** and **9** resemble 2,4,6-triisopropylphenyl 2,4,6-triisopropylbenzenethiolsulfinate, which seems considerably more stable than is usual for thiolsulfinates and which could not be oxidized to the dioxide; the corresponding 2,4,6-triisopropylphenyl disulfide resembled **6** and **7** in resisting oxidation (*cf.* ref 5). These characteristics in the triisopropylphenyl series were attributed to steric factors. The resistance of **6–9** toward oxidation to 1,1-dioxides probably has its explanation in steric or conformational factors also (perhaps, for example, to resistance to a necessary ring inversion of conformers during the two-stage oxidation).

A report that sodium metaperiodate in *methanol* will oxidize a sulfide to a sulfone ultimately proved the key to successful preparation of the 1,1-dioxide **10**,[6] and in initial studies **10** was obtained in fairly good yield (60%) by using aqueous 2-propanol as solvent for the reaction of **6** with potassium metaperiodate (80°, 49 hr; the ir peak for –SO– persisted at 30 hr). With aqueous methanol, **6** was oxidized to **10** but in only 28% yield (40 hr); with a short reaction time (3 hr), the yield of **10** was 48%. Potassium metaperiodate rather than the sodium salt was used because it had given better results with 1,2-dithiane.[3a] Nmr, ir, and mass spectra and elemental analyses met expectation for **10**.

During the successful oxidation of **6** to **10** in aqueous 2-propanol, the mixture slowly became brown. Loss of the color when the product was washed with aqueous sulfite suggested that iodine was responsible for the color and led to the suspicion that the reaction might have been autocatalytic, with the iodine generated serving as a catalyst. This suspicion was confirmed by estimating the amounts of monoxide **8** and dioxide **10** present as a function of time when increasing amounts of iodine were used (see Experimental Section). The time required for complete loss of ir absorption attributable to the –SO– moiety (and for appearance of that of the $-SO_2-$ moiety) varied with the molar proportion of iodine (in parentheses) as follows: 33 (0), 16 (0.02), 9 (0.04), and 6.5 hr (0.08). Hence I_2 is indeed quite effective as a catalyst. This usefulness of alcohols and iodine under vigorous conditions in a periodate oxidation appears to be an exciting lead. Further exploration of the combination KIO_4–*i*-PrOH–H_2O–I_2 as a tool for oxidizing –S– moieties of both sulfides and disulfides to $-SO_2-$ moieties seems called for, and it seems likely that studies of the mechanism also would lead to rewarding results. When iodine catalysis was used preparatively with potassium metaperiodate to oxidize **6** in *i*-PrOH–MeOH–H_2O, **10** was obtained in a yield of 67% after 7 hr of reflux (0.02 mol of I_2/mol of **6**).

Earlier work on the cleavage of 1,2-dithiane 1,1-dioxide (**12**) by nucleophiles revealed that such "oxodisulfide" cleavages can lead to useful syntheses of disulfides terminated with the moieties $-SO_2^-$, $-SO_3^-$, $-SO_2R$, and $-SO_2SR$.[3b] In further studies of the generality of cleavage, hydride and halide ion cleavages were found to be unpromising in the solvents tried.[1a] Similarly, we have now been unable to see that morpholine or piperidine effect any useful degree of cleavage, even though amines are known to cleave certain acyclic thiolsulfonates.[7] Thus when **12** was heated under reflux in benzene, methylene chloride, or tetrahydrofuran with these amines for 21–24 hr it was recovered quantitatively in each instance; presumably, under the conditions used, the equilibrium constant for cleavage was quite unfavorable (*cf.* ref 7). On the other hand, the sodium salt of 2-acetamidoethanethiol (**13**) smoothly cleaved the dioxide **10** to give the disulfide sulfinate **14** in 73% yield (eq 1). Nmr and ir spectra are consistent

$$\underset{\mathbf{13}}{AcNH(CH_2)_2SH} \xrightarrow{NaOEt} AcNH(CH_2)_2SNa$$

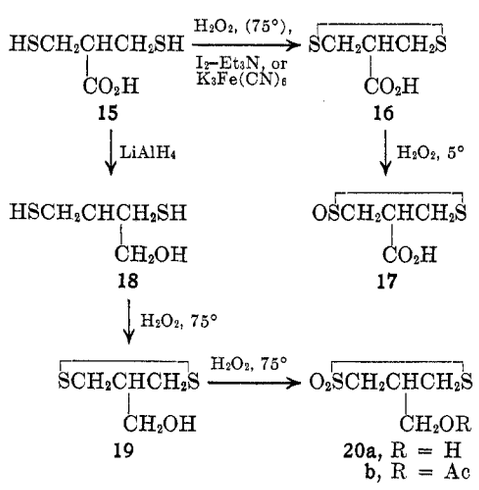
$$AcNH(CH_2)_2SNa \xrightarrow[-10°]{EtOH\text{-}Me_2CO,\ \mathbf{10}} \underset{\mathbf{14}}{AcNH(CH_2)_2SSCH_2CH(OAc)CH(OAc)CH_2SO_2Na} \quad (1)$$

with the formulation of product as **14**, as is the analogy of a similar reaction with 1,2-dithiane 1,1-dioxide (**12**).[1a,3b]

Scheme II shows the results of studies with 1,2-dithiolanes. The dithiol **15** was oxidized previously to 1,2-dithiolane-4-carboxylic acid (**16**) by use of oxygen and ferric chloride (overall yield from β,β′-diiodoiso-

(5) L. Field and T. F. Parsons, *J. Org. Chem.*, **30**, 657 (1965).
(6) L. L. Replogle and J. R. Maynard, *J. Org. Chem.*, **32**, 1909 (1967).
(7) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).

SCHEME II



butyric acid, 17%).[8] 1,2-Dithiolane itself has been synthesized in good yield by adding the thiol and hydrogen peroxide simultaneously but separately to acetic acid containing a little KI at 75°,[3a] and use of this procedure with **15** gave **16** in yields of 57–85%. Use of I_2–Et_3N, which often gives good results in cyclization of α,ω-dithiols,[3a,9] led to **16** in 40% yield, and use of potassium ferricyanide, which was effective for synthesis of the dithianes **3** and **4**,[10] gave **16** in 32% yield. We were able to confirm the experience of Lindberg and Bergson in being able to convert the dithiolane **16** to the monoxide **17** (72% yield; 63% reported).[11] Unfortunately, we also confirmed their experience in being unable to obtain the 1,1-dioxide of **16**; the hydrogen peroxide–tungsten trioxide procedure,[5] as well as KIO_4 in H_2O or aqueous 2-propanol (with **16** or its sodium salt), seemed to lead only to cleavage to sulfonic acids (pH ~1–2) and to polymerization.

Lindberg and Bergson succeeded in oxidizing 4,4-bis(hydroxymethyl)-1,2-dithiolane to the 1,1-dioxide by the use of hydrogen peroxide.[11] Although the *gem*-methylol moieties may well have stabilized this dioxide, in common with frequently observed effects of groups on otherwise unstable ring systems, we considered the sequence of **18** → **19** → **20a** worth exploration (Scheme II). The acid **15** therefore was reduced to the carbinol **18** (70% yield), which was oxidized to a liquid that polymerized readily but was presumed from spectra to be largely **19** (~70% yield). Oxidation of a sample of **19** without delay did seem to give a dioxide, but spectra indicated that the product was the acetate **20b** rather than the carbinol **20a** (see Experimental Section); if the assignment of structure **20b** to the product is correct, esterification of **20a** to **20b** is understandable, since reaction of acetic acid used as solvent with the carbinol **20a** could have been catalyzed by sulfonic acids produced by cleavage of the ring. This reaction was not investigated further because it was not very clean and because the yield was low.

Results available thus far for compounds tested as antiradiation drugs are unpromising.[12] Compounds, LD_{50} (mg/kg), doses (mg/kg), per cent of survival of mice after 30 days, and antiradiation ratings, respectively, were as follows: **3**, 450, 250, 0, inactive; **6**, 750, 200, 13 (17-day survival), slight; **8**, 120, 25–50, 7–13, slight.

Experimental Section[13]

Starting Materials.—Commercial dithiothreitol (**1**) and dithioerythritol (**2**) (N. B. C. Research Biochemicals) were used after checking them by ir and nmr, and 2-mercaptomethyl-3-mercaptopropionic acid (**15**) was kindly supplied by Dr. D. L. Klayman of the Walter Reed Army Institute of Research, Washington, D. C. 2-Acetamidoethanethiol (**13**) was prepared as reported.[14]

1,2-Dithiane-4,5-diols, *trans*- (**3**) **and** *cis*- (**4**), were prepared by oxidizing **1** and **2**, respectively, with $K_3Fe(CN)_6$[10] and recrystallizing the products from EtOAc; yield of **3**, 75%, mp 133–134° (lit.[10] mp 132°); yield of **4**, 70%, mp 132–133° (lit.[10] mp 132°).

1,2-Dithiane-4,5-diol Diacetate, *trans*- (**6**) **and** *cis*- (**7**).—Well dried and powdered trans diol **3** (15.0 g, 0.0987 mol) was added slowly to acetyl chloride (23.4 g, 0.298 mol) with good stirring at 0–5°. The mixture boiled spontaneously during the first part of the reaction. After stirring had been continued for 3 hr at ~25°, clear liquid resulted. $CHCl_3$ (200 ml) then was added, and the solution was poured into 100 ml of water containing 200 g of ice. The organic layer was well shaken with 100 ml of iced saturated aqueous Na_2CO_3 solution and then with cold H_2O until it was neutral. It was dried and concentrated to 22.0 g (94%) of oil, which gradually solidified at 0°. Recrystallization by dissolution in Et_2O at 25°, addition of *n*-hexane to incipient turbidity, and chilling at 0° gave 19.0 g (82%) of **6**, mp 43–49°. Further recrystallization from Et_2O gave **6** as white plates: mp 52–53° (lit.[4] mp 54–55°); nmr ($CDCl_3$) δ 2.07 (s, CH_3CO), 3.19–3.03 (m, CH_2), 5.15–4.90 (m, OCH).

Anal. Calcd for $C_8H_{12}O_4S_2$: C, 40.70; H, 5.09; S, 27.18. Found: C, 40.92; H, 5.10; S, 27.35.

Essentially by the same procedure, *cis*-1,2-dithiane-4,5-diol (**4**, 0.65 g, 4.27 mmol) and AcCl (1.00 g, 12.80 mmol) gave the cis diacetate **7** (0.75 g, 74%): mp 73–74° (lit.[4] mp 74–75°); nmr ($CDCl_3$) δ 2.03 (s, CH_3CO), 3.22–2.95 (m, $-CH_2-$), 5.15–4.96 (m, OCH).

trans-**1,2-Dithiane-4,5-diol Diacetate 1-Monoxide** (**8**). **A.** *Via* **Potassium Metaperiodate** (KIO_4).—The diacetate **6** (10.0 g, 42.4 mmol) in 100 ml of Me_2CO was added to a solution of KIO_4 (40.0 g, 174.0 mmol) in 300 ml of H_2O. After this heterogeneous reaction mixture had been stirred for 5 days, it was heated at 60° for 4 hr and was filtered to remove KIO_4.

The filtrate was concentrated to 100 ml and then extracted with $CHCl_3$ three times. The $CHCl_3$ extract was washed with cold H_2O and concentrated to give 9.1 g (85%) of crude **8**, mp 110–145°. Recrystallization by dissolution in benzene at ~40°, addition of *n*-hexane to incipient turbidity, and standing at 25° overnight, and then further recrystallization from benzene, gave **8** as white plates of constant mp 150–151°: nmr ($CDCl_3$) δ 2.04 (s, CH_3CO), 2.11 (s, CH_3CO), 3.98–2.80 (m, CH_2), 6.02–5.03 (m, CH); ir 1750, 1375, 1250, 1240, 1060 and 1030 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 70 (45), 84 (45), 112 (35), 132 (8), 150 (4), 172 (6), 252 (3).

(8) L. Schotte and H. Ström, *Acta Chem. Scand.*, **10**, 687 (1956). A referee kindly pointed out a recent modification that affords **16** from **15** in ~90% yield [J. P. Danehy and V. J. Elia, *J. Org. Chem.*, **37**, 369 (1972)].

(9) D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **35**, 3259 (1970).

(10) W. W. Cleland, *Biochemistry*, **3**, 480 (1964).

(11) B. Lindberg and G. Bergson, *Ark. Kemi*, **23**, 319 (1965).

(12) 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. For details of procedures, see ref 1a and other papers cited therein.

NOTE ADDED IN PROOF.—The two enantiomers of **3** were recently reported to have LD_{50} = 410 and 435 mg/kg and not to be protective at doses of 200–300 mg/kg against 625–750 R of radiation [M. Carmack, C. J. Kelley, S. D. Harrison, Jr., and K. P. DuBois, *J. Med. Chem.*, **15**, 600 (1972)].

(13) Melting points are corrected, and boiling points are uncorrected. Mass spectra were obtained with an LKB Model 9000 instrument operated at 70 eV with a source temperature of 250° and an accelerating potential of 3.5 kV, using the direct-probe inlet; this instrument was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to C. T. Wetter for these spectra. Moist extracts ordinarily were dried over anhydrous $MgSO_4$, and solvent then was removed using a rotating-flask evaporator. The ratios of nmr integrals met expectation and therefore are not reported. Other details were as given in footnote 6 of ref 1a.

(14) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

Anal. Calcd for $C_8H_{12}O_5S_2$: C, 38.08; H, 4.77; S, 25.41; mol wt, 252. Found: C, 38.38; H, 4.84; S, 24.98; mol wt, 252 (mass spectrum).

B. *Via* **Hydrogen Peroxide.**—A solution of ~30% H_2O_2 (2.5 mmol) in glacial AcOH (2 ml) was added to **6** (0.44 g, 1.87 mmol) in glacial AcOH (2 ml) with stirring at 25°. Stirring was continued for 3 hr at 25°. After removal of solvent, addition of cold H_2O resulted in white crystals. Filtration gave 0.30 g of **8** (64%), mp 150–151°; the nmr and ir spectra corresponded to those of **8** from **A**.

C. *Via* **Potassium Permanganate.**—A solution of $KMnO_4$ (0.20 g, 1.27 mmol) in Me_2CO (10 ml) was added to **6** (0.100 g, 0.43 mmol) in Me_2CO (5 ml). The mixture was heated under reflux for 5 hr and then was allowed to stand for 10 hr at ~25°. Removal of solvent and extraction of the residue with $CHCl_3$ gave 0.04 g (38%) of **8**, mp 150–151°.

D. *Via* **Chromium Trioxide.**—A solution of CrO_3 (2.1 mmol) in ~8 *N* H_2SO_4 was added to **6** (0.11 g, 0.47 mmol) in Me_2CO (10 ml). The heterogeneous mixture was stirred for 18 hr at ~25° and then was diluted with $CHCl_3$. Insoluble solid was removed, and the $CHCl_3$ layer was washed with cold H_2O, dried, and concentrated, leaving a mixture (0.08 g) of disulfide **6** and monoxide **8**.

cis-**1,2-Dithiane-4,5-diol Diacetate 1-Monoxide** (**9**).—The cis diacetate **7** (0.70 g, 2.96 mmol) in Me_2CO (60 ml) was added to a solution of KIO_4 (3.10 g, 13.5 mmol) in H_2O (120 ml). After this heterogeneous mixture had been stirred for 68 hr at ~25°, the volume was reduced to about 10 ml, and the mixture was extracted with benzene. The extract was dried and evaporated to give **9**, 0.60 g (80%), mp 112–114°. Recrystallization from *n*-hexane and then from benzene gave **9** as white crystals of constant mp 113–114°: nmr ($CDCl_3$) δ 2.11 (s, CH_3CO), 2.21 (s, $-CH_3CO$), 4.20–3.26 (m, $-CH_2-$), 5.93–5.41 (m, OCH); ir 1745, 1370, 1240, 1200, 1065, 1045, 1030 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 70 (45), 84 (35), 112 (40), 132 (4), 150 (4), 172 (7), 252 (3).

Anal. Calcd for $C_8H_{12}O_5S_2$: C, 38.08; H, 4.77; S, 25.41; mol wt, 252. Found: C, 37.90; H, 4.75; S, 25.80; mol wt, 252 (mass spectrum).

trans-**1,2-Dithiane-4,5-diol Diacetate 1,1-Dioxide** (**10**). **A.** *Via* **KIO_4 in *i*-PrOH.**—A solution of the trans diacetate **6** (6.4 g, 27.1 mmol) in *i*-PrOH (500 ml) was added to KIO_4 (18.57 g, 80.6 mmol) in H_2O (140 mmol). After the heterogeneous reaction mixture has been heated at 80–82° for 30 hr with good stirring, a small portion of solution was withdrawn to check for complete oxidation to the dioxide **10** by ir; the monoxide peak at 1060 cm^{-1} still remained. After 49 hr, the mixture had become brown and showed only strong dioxide-peak absorption at 1310 and 1110 cm^{-1}, with no peak at 1060 cm^{-1}. After removal of the *i*-PrOH and H_2O, the residue was extracted with $CHCl_3$ three times. The extract then was washed with 10% aqueous Na_2SO_3 solution to remove I_2. The extract was washed again with H_2O, dried, and evaporated to give **10**, yield 4.4 g (60%), mp 133–139°. Recrystallization from benzene gave **10** as white needles having a constant mp of 140–142°; nmr ($CDCl_3$) δ 2.18 (s, CH_3CO), 2.22 (s, CH_3CO), 3.90–3.51 (m, $-CH_2$), 5.60–5.08 (m, OCH); ir 2980, 1740, 1720, 1360, 1310, 1220, 1110, 1030, 860, 760 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 84 (33), 101 (8), 148 (3), 208 (1).

Anal. Calcd for $C_8H_{12}O_6S_2$: C, 35.82; H, 4.48; S, 23.85. Found: C, 35.79; H, 4.52; S, 23.68. In another experiment, a 24-hr reflux period led to **10** in 69% yield.

B. *Via* **KIO_4 in MeOH.**—From the reaction of **6** (0.128 g, 0.54 mmol) in 10 ml of MeOH with KIO_4 (0.36 g, 1.56 mmol) in H_2O (3 ml) at 80° for 40 hr, **10** was obtained (after recrystallization from benzene) as white needles, 0.040 g (28%), mp 140–142°. Experiments like those described in C with *i*-PrOH showed that only 3 hr actually was necessary for complete loss of the –SO– peak, and a shorter reaction period of 3 hr gave **10** in 48% yield.

C. *Via* **KIO_4 in *i*-PrOH–H_2O Containing I_2.**—In order to learn whether I_2 was an effective catalyst, experiments were done using the different amounts of I_2 shown in Table I. For example, a mixture of **6** (177 mg, 0.75 mmol) in *i*-PrOH (16 ml) with KIO_4 (540 mg, 2.34 mmol) in H_2O (5 ml) was heated at 80–82° with good stirring. From time to time, ~1.5 ml of solution was withdrawn and was concentrated and extracted with $CHCl_3$. After the extract had been dried and the $CHCl_3$ removed, the residue was used directly as an ir sample. The percentages of the dioxide **10** and monoxide **8** were approximated by comparing intensities at 1110 and 1060 cm^{-1}, respectively, with those of authentic samples (by use of a plot for **8** and another for **10** in which intensity had been normalized to a constant value for –CHO– at 1030 cm^{-1} and then plotted *vs.* per cent of **8** and **10**). The results are shown in Table I; concentrations and amounts were the same in all experiments as those given above, except for I_2.

TABLE I

OXIDATION OF *trans*-1,2-DITHIANE-4,5-DIOL DIACETATE (**6**) WITH KIO_4 IN AQUEOUS *i*-PrOH AT ~80°

Mol of I_2 / Mol of **6**	Time, hr	Estimated composition of products, % **8**	**10**
0	12	95	5
	16	80	20
	21	55	45
	26	25	75
	33	0	100
0.02	5	90	10
	6	60	40
	8	50	50
	11	10	90
	16	0	100
0.04	3	90	10
	5	60	40
	8	10	90
	9	0	100
0.08	1	75	25
	3	55	45
	5	5	95
	6.5	0	100

In a preparative experiment, a mixture of 18.0 g of **6**, 52.6 g of KIO_4, 0.386 g of I_2, 200 ml of *i*-PrOH, 100 ml of MeOH, and 300 ml of H_2O was heated at 80° with good stirring for 7 hr. The yield of **10**, isolated as a white solid of mp 133–139°, was 13.6 g (67%).

cis-**1,2-Dithiane-4,5-diol Diacetate 1,1-Dioxide** (**11**).[15]—A mixture of the dithiane **7** (0.20 g, 0.85 mmol) in Me_2CO (20 ml) and of KIO_4 (0.80 g, 3.48 mmol) in H_2O (40 ml) was kept at 40° for 50 hr and then was let stand at ~25° for 24 hr. A $CHCl_3$ extract gave 0.15 g (66%) of **11**, mp 145–150°. Recrystallization from benzene gave **11** of constant mp 153–154°: nmr ($CDCl_3$) δ 2.11 (s, CH_3CO), 2.21 (s, CH_3CO), 3.86–3.48 (m, CH_2), 5.35–5.66 (m, OCH); ir 1750, 1370, 1320, 1220, 1200, 1120, 1040, 955, and 775 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 84 (55), 101 (15), 148 (5), 208 (2).

Anal. Calcd for $C_8H_{12}O_6S_2$: C, 35.82; H, 4.48; S, 23.85. Found: C, 35.72; H, 4.49; S, 24.00.

Sodium 4-(2-Acetamidoethyldithio)butane-2,3-diol-1-sulfinate Diacetate (**14**).[16]—A 0.5 *N* solution of NaOEt (40.0 ml, 20.0 mmol) was added to the thiol **13** (2.44 g, 20.5 mmol) in EtOH (20 ml) at 0° (the pH then was ~8). This solution of the thiolate was added during ~1 hr to a solution of **10** (5.36 g, 20 mmol) in a mixture of Me_2CO (50 ml) and EtOH (20 ml) at ~−10° with stirring (pH ~6.5). Dry Et_2O (700 ml) then was added until no more precipitate appeared, and the mixture was kept at 0° for 5 hr. Most of the solvent was decanted, and the precipitate was dried at 25° (0.1 mm). The dry white **14** was dissolved in Me_2CO. A small amount of insoluble solid was removed by centrifugation, and Et_2O was added to precipitate **14**. Et_2O was decanted, and residue was dried at 25° (0.1 mm) for 10 hr; yield of **14**, 6.0 g (73%), mp ~99° dec. Similarly prepared **14** (identical ir spectrum) was characterized: nmr (D_2O) δ 2.15–2.31 (CH_3CO), 2.60–3.66 (m, CH_2), 5.33–5.65 (m, OCH); ir 3260 (broad) 1730, 1640, 1540, 1430, 1375, 1220, 1020, 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}NNaO_7S_3$: C, 35.20; H, 4.91; N,

(15) This reaction succeeded only once. Use of the same conditions twice more resulted in no **11**. It seems likely, however, that one of the procedures that later gave the trans isomer (**10**) will succeed. Synthesis of the trans dioxide **10** sufficed at present for chemical and biological studies and, unless biological results warrant, we plan no further studies with the cis isomer **11**.

(16) This procedure was based on one for the reaction of the salt of **13** with 1,2-dithiane 1,1-dioxide (**12**),[3b] but it includes important modifications discussed in ref 1a.

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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 2.12 [s, CH_3-C(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.

(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).

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]

YONG H. KHIM AND LAMAR FIELD*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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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 ω-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

(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).