Organic Disulfides and Related Substances. XXX. Preparations and Reactions of Mercaptoterephthalic Acids and Derivatives[1]

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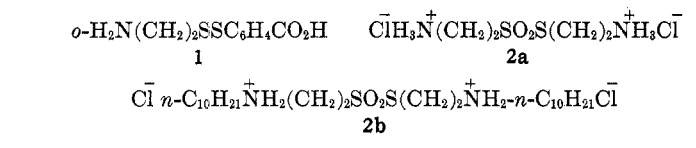
2,5-Dimercaptoterephthalic acid was prepared by four routes to permit assessment of their relative merits for a bifunctional system and to permit confirmation of structures of useful intermediates through interconnections of the routes (Scheme I). The routes were: (I) conversion of the phenol to the *O,O*-bisthiocarbamate, rearrangement of this to the *S,S*-bisthiocarbamate, then saponification; (II) cleavage of 2,5-bisbenzyl thioether moieties of the terephthalate diester, then saponification; (III) reaction of potassium hydrosulfide with 2,5-dibromoterephthalic acid; and (IV), route II but with the acid instead of the ester. 2-Mercaptoterephthalic acid was prepared by similar routes for the same reasons. Both the mono- and dimercapto acids reacted with aminoalkyl thiolsulfonates to give unsymmetrical aminoalkyl disulfides (Scheme II). Several products of Schemes I and II are of interest for further chemical studies and, particularly, for biological evaluation as antiradiation drugs, against histoplasmosis, or against schistosomiasis.

Mercaptoterephthalic acids were desired for two reasons: (1) *o*-(2-Aminoethyldithio)benzoic acid (**1**) and



related compounds have shown activity as antiradiation drugs.[2a-c] Bis and 4-carboxy analogs of **1** were needed for assessing the effects that structural changes of these kinds would have on antiradiation activity and toxicity. Furthermore, arenethiols and aryl disulfides seem promising classes for testing against *Histoplasma capsulatum*,[2d] the causative organism of histoplasmosis, and possibly against schistosomiasis.[2e] Since **1** was prepared by thioalkylating *o*-mercaptobenzoic acid with the thiolsulfonate **2a**,[2a] the use of **2a** and **2b** with 2,5-dimercaptoterephthalic acid and 2-mercaptoterephthalic acid (**12** and **15**, respectively, of Scheme I) seemed likely to give bis and 4-carboxy analogs of **1** (**23**–**25** of Scheme II). (2) The 1,4-benzenedithiol system has quite interesting chemical possibilities. Oxidation of 2,5-dimercaptoterephthalic acid or its ester (**12** and **19** of Scheme I) might give thioquinones, tetrathia[2.2]paracyclophanes, or polymers; Parekh and Guha oxidized 1,4-benzenedithiol to a solid they thought might be tetrathia[2.2]paracyclophane, but the insolubility of their product also suggests it may have been polymeric.[3] Furthermore, reaction of 1,4-diethoxybenzene with sulfur monochloride gave a large-ring crystalline polysulfide,[4] which has attracted considerable interest;[4b] **12** should afford further entries into such systems.

Scheme I shows approaches to the synthesis of 2,5-dimercaptoterephthalic acid (**12**) and 2-mercaptoterephthalic acid (**15**) by four routes, I–IV. Interconnections between routes I–IV, made primarily to buttress the structure of intermediates, also provide conversions useful for connecting the routes during other work with mercaptoarenecarboxylic acids. The four routes are: (I) conversion of phenols to thiophenols *via* thiocarbamates; (II) cleavage of benzyl (alkoxycarbonyl)aryl sulfides; (III) reaction of potassium hydrosulfide with bromoterephthalic acids; and (IV) cleavage of benzyl carboxyaryl sulfides.

2,5-Dibromoterephthalic acid (**3**) was the starting material for all routes. For preparation of **3**, oxidation failed of 2,5-dibromo-*p*-xylene with nitric acid[5] and with potassium dichromate in sulfuric acid[6] or acetic acid. Oxidation of *p*-xylene with bromine[7] or of 2,5-dibromo-*p*-xylene with permanganate gave **3**, but in low yield. Sodium dichromate,[8] however, oxidized 2,5-dibromo-*p*-xylene to acid **3** in yields of 57–64%.

Route I.—Route I was the best of the four for the preparation of dithiol **12**. After the salt of acid **3** (from **3** in ethanolic sodium ethoxide, 97%) had been heated with sodium acetate and copper powder, acidification gave 2,5-dihydroxyterephthalic acid (**4**, 97% yield),[9] which was converted to the diester **5** (57% yield);[10] substitution of the commercially available 2,5-dichloroterephthalic acid led only to diethyl 2,5-dichloroterephthalate.

A modification of the elegant conversion of Newman and Karnes of phenols to thiophenols[11] next was used. The dihydroxy ester (**5**) gave the *O,O*-bisthiocarbamate **6** in 88% yield; **6** had ir bands characteristic for C(=S)N and C(=S) and two nmr singlets for NMe_2 (δ 3.43, 3.48). The rearrangement of **6** to the *S,S*-bisthiocarbamate **13** went smoothly at 230° (76%); higher temperatures led to unnecessary decomposition. The

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(1) (a) Paper XXIX: N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts No. DA-49-193-MD-2030 and DADA17-69-C-9128. (c) Abstracted from the Ph.D. Dissertation of P. R. E. (Vanderbilt University, May 1970), which may be consulted for further details. (d) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967.

(2) (a) R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965). (b) L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970); the "proto" nomenclature used for **1** and analogs in this earlier paper was less well adapted to the present paper. (c) L. Field and H. K. Kim, *ibid.*, **9**, 397 (1966). (d) I. McVeigh, Z. Evans, L. Field, and W. Hanley, *Mycopathol. Mycol. Appl.*, **37**, 349 (1969). (e) We are indebted to Dr. E. A. Steck of the Walter Reed Army Institute of Research for this suggestion.

(3) V. C. Parekh and P. C. Guha, *J. Indian Chem. Soc.*, **11**, 95 (1934).

(4) (a) Z. S. Ariyan and R. L. Martin, *Chem. Commun.*, 847 (1969). (b) *Cf. Chem. Eng. News*, **47** (No. 48), 40 (Nov 17, 1969).

(5) *Cf.* A. Eckert and F. Seidel, *J. Prakt. Chem.*, **102**, 338 (1921).

(6) *Cf.* R. Fittig, W. Ahrens, and L. Mattheides, *Justus Liebigs Ann. Chem.*, **147**, 15 (1868).

(7) J. E. McIntyre and D. A. S. Ravens, *J. Chem. Soc.*, 4082 (1961).

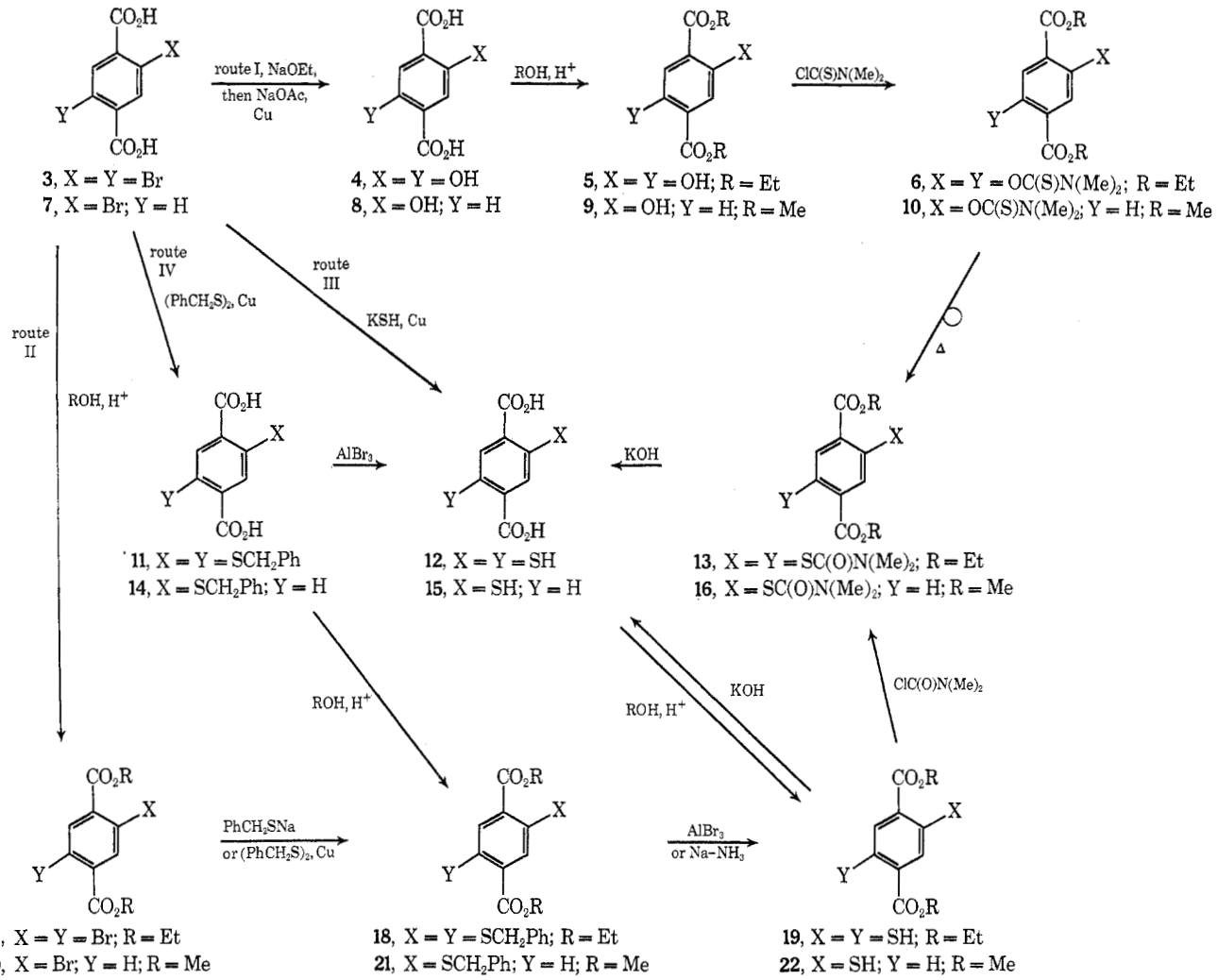
(8) L. Friedman, D. L. Fishel, and H. Shechter, *J. Org. Chem.*, **30**, 1453 (1965).

(9) A. Marzin, *J. Prakt. Chem.*, **138**, 103 (1933).

(10) K. Brunner, *Justus Liebigs Ann. Chem.*, **351**, 313 (1907).

(11) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).

SCHEME I



3, X = Y = Br
7, X = Br; Y = H
4, X = Y = OH
8, X = OH; Y = H
5, X = Y = OH; R = Et
9, X = OH; Y = H; R = Me
6, X = Y = OC(S)N(Me)2; R = Et
10, X = OC(S)N(Me)2; Y = H; R = Me
11, X = Y = SCH2Ph
14, X = SCH2Ph; Y = H
12, X = Y = SH
15, X = SH; Y = H
13, X = Y = SC(O)N(Me)2; R = Et
16, X = SC(O)N(Me)2; Y = H; R = Me
17, X = Y = Br; R = Et
20, X = Br; Y = H; R = Me
18, X = Y = SCH2Ph; R = Et
21, X = SCH2Ph; Y = H; R = Me
19, X = Y = SH; R = Et
22, X = SH; Y = H; R = Me

S,S-bisthiocarbamate **13** had an ir band typical of an amide and only an nmr singlet for NMe_2 (δ 3.1, two nmr peaks for the *N*-methyl groups of *O*-aryl compounds, but only one for those of *S*-aryl compounds, were observed previously).[11]

The last step in route I was saponification of **13** to the dithiol **12**. Newman and Karnes effected saponification of *S*-aryl thiocarbamates in hot aqueous methanol under nitrogen, but, when **13** was similarly heated for 9 hr (when iodine uptake became constant), the product appeared to be oxidized **12**, iodine titration indicating that only one thiol group of **12** had survived. Eventually, we learned that heating of the *S,S*-bisthiocarbamate **13** with potassium hydroxide (in slight excess of six molar proportions) at 120–130° for 20 min would give the dithiol **12** in 100% yield. This rather critical time of heating was determined by titrating aliquots with acid until a plot of acid consumption reached a minimum; after 20 min the acid increased, suggesting that oxidation was taking place.

The structure of **12** was confirmed by iodine titration. The ir spectrum was consistent. The nmr spectrum, done in *N,N*-dimethylacetamide (DMA) because of sparing solubility in the usual solvents, showed a singlet (δ 8.2) for the ring protons, with the acid and thiol protons either obscured in the base line or buried beneath the solvent peaks; exchange with D_2O, however, led to a peak at δ 4.8 for HOD and a 2:1 ratio for the integrals at δ 4.8 and 8.2 which supported the dithiol structure for **12**. The mass spectrum of **12** showed the molecular ion at *m/e* 230, with peaks and metastables (*) consistent with the events formulated in eq 1; *o*-

$$\underset{(12)}{m/e\ 230\ (M^+)} \xrightarrow[(m/e\ 195.4^*)]{-H_2O} m/e\ 212 \xrightarrow[(m/e\ 177.5^*)]{-H_2O} m/e\ 194 \xrightarrow[(m/e\ 142.1^*)]{-CO} m/e\ 166 \xrightarrow[(m/e\ 114.7^*)]{-CO} m/e\ 138 \quad (1)$$

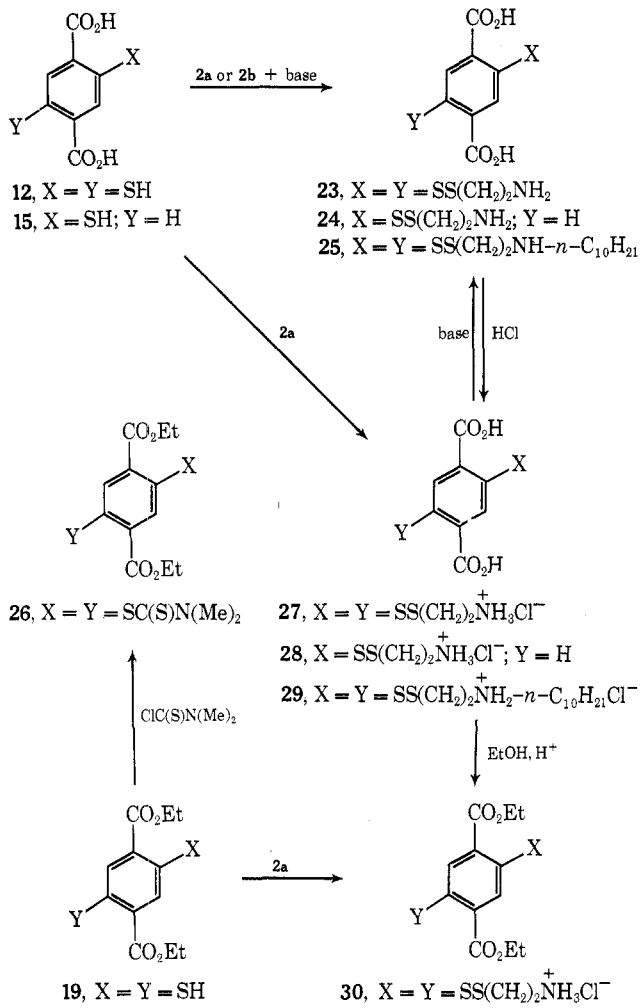
mercaptobenzoic acid shows similar behavior.[12] Consistent with the strong yellow color of **12** (and of about a third of the other compounds in Schemes I and II) is a low order of absorption of **12** at 435–470 nm (**12** also had λ_{max} at 276 and 375 nm).

Toward the preparation of the monomercapto acid **15** by route I, sodium 2-bromoterephthalate gave 2-hydroxyterephthalic acid (**8**, 99%), which was converted to the ester **9** (77% yield; the dimethyl ester was used because it was known).[13] *N,N*-Dimethylthiocarbamoyl chloride converted **9** to the monothiocarbamate **10**. Although **10** did not precipitate as had the bisthiocarbamate **6**, addition of water gave a 92–97% yield, but the

(12) S.-O. Lawesson, J. Ø. Madsen, G. Schroll, J. H. Bowie, and D. H. Williams, *Acta Chem. Scand.*, **20**, 2325 (1966).

(13) R. Wegscheider and K. Bittner, *Monatsh. Chem.*, **21**, 638 (1900).

SCHEME II



carbamoyl chloride then had to be removed by recrystallization. The ir spectrum of **10** indicated C(=S)N and C(=S), and the nmr spectrum again showed two singlets (δ 3.42, 3.47). Rearrangement of **10** to **16** was accomplished as with **6**. Conversion of **16** to the acid **15** was not tested because **16** was not obtained completely pure and because by this time route II to **15** was considered better than route I; the successful conversion of **13** to **12** suggests that conversion of **16** to **15** should present no difficulties.

Route II.—In route II to the dithiol **12** and thiol **15** bromine atoms were replaced with benzyl thioether moieties, and the benzyl groups then were removed. Preparation of the benzyl sulfides **18** and **21** by the usual use of cuprous phenylmethanethiolate with the bromo esters **17** and **20** was precluded because, unlike other cuprous thiolates, cuprous phenylmethanethiolate decomposes into benzyl sulfide and stilbene before reacting with an aryl halide.[14] We therefore turned to two procedures of Campbell.[15,16] The first involves direct action of a disulfide on an aryl halide in the presence of copper[15] and the second heating of an alkali-metal thiolate with the halide.[16] When the dibromo diester **17** was heated with benzyl disulfide and copper, yields of the bisbenzyl sulfide **18** were 29–33% and, on a larger scale, even dropped to 5%. As a prelude to the more promising second approach, the stability of sodium phenylmethanethiolate in DMA was tested. At 100°, the solution soon darkened and, after 7 hr, failed to decolorize iodine. Hence the ester **17** and the thiolate were heated only at 75° (24 hr); the yield of **18** was 50%. Substitution of the commercially available 2,5-dichloroterephthalic acid (same molar proportions) for **3** in route II led to **18** in overall yields nearly as good as those from **3**.

Removal of the benzyl groups of **18** was accomplished in two ways. Use of sodium in liquid ammonia[17] gave **19**, which decolorized iodine and had appropriate ir and nmr spectra, but no way could be found to purify it. Hence cleavage with aluminum bromide in dry toluene was used.[18] Ultimately, **18** was cleaved thus to the dithiol **19** in 76% yield; substitution of chlorobenzene[19] for toluene resulted in a yield of 60%. In early work, the ir spectrum of crude **19** showed the presence of both carboxyl and benzyl groups, suggesting partial hydrolysis of the ester and incomplete cleavage of the sulfide. Purification of the aluminum bromide[20] failed to prevent the hydrolysis (but even so is desirable because it leads to purer thiol), but predistillation of the toluene from phosphorus pentoxide did so.

The structure of the dimercapto diester **19** was confirmed by ir absorption for SH, by iodine titration, and by the mass spectrum. The mass spectrum is consistent with the events of eq 2, which resemble those of

$$\underset{(19)}{m/e\ 286\ (M^+)} \xrightarrow[(m/e\ 201.4^*)]{-EtOH} m/e\ 240 \xrightarrow[(m/e\ 156.8^*)]{-EtOH}$$
$$m/e\ 194 \xrightarrow[(m/e\ 142.1^*)]{-CO} m/e\ 166 \xrightarrow[(m/e\ 114.7^*)]{-CO} m/e\ 138 \quad (2)$$

eq 1 for the diacid **12**; similar behavior has been reported for methyl *o*-mercaptobenzoate.[12] For further substantiation, route II was connected with route I by converting the dimercapto diester **19** of route II to the *S*,*S*-bisthiocarbamate **13** (69%).

The final step in route II was saponification of **19** to the diacid **12** (quantitative yield); when saponification was incomplete, purification was very difficult. The overall yield of **12** from **3** by the four steps of route II was about 32%; although there is also a somewhat better yield, route I (overall yield from **3** about 36%) was recommended above, despite its six steps, mainly because all steps are easily done and the overall process seems easier.

Route II seems that of choice for preparation of the monomercaptoacid **15** because it is shorter than route I and involves products usually easier to purify (overall yield from **7**, 18%). For the preparation of **15** by route II, dimethyl 2-bromoterephthalate (**20**)[13] was converted to the sulfide **21** with sodium phenylmethanethiolate. Cleavage of **21** with aluminum bromide always gave both the diester **22** and acid, despite distillation of the toluene from phosphorus pentoxide and other precautions to exclude moisture and irrespective of the amount of aluminum bromide or of whether it was purified;[20] probably the unhindered 4-carboxylate moiety of **21** is more susceptible to attack by aluminum bromide

(14) R. Adams and A. Ferretti, *J. Amer. Chem. Soc.*, **81**, 4927 (1959).
(15) J. R. Cambell, *J. Org. Chem.*, **27**, 2207 (1962).
(16) J. R. Campbell, *ibid.*, **29**, 1830 (1964).
(17) A. Ferretti, *Org. Syn.*, **42**, 54 (1962).
(18) A. E. Lanzilotti, J. B. Ziegler, and A. C. Shabica, *J. Amer. Chem. Soc.*, **76**, 3666 (1954).
(19) D. S. Tarbell and D. P. Harnish, *ibid.*, **74**, 1862 (1952).
(20) C. F. H. Tipper and D. A. Walker, *J. Chem. Soc.*, 1352 (1959).

than the more hindered carboxylate moieties of **18**. Saponification of the mixture of monomercapto ester and acid gave the thiol **15** (55% from **21**).

Route III.—Route III to the dimercapto acid **12** involved the single reaction of eight molar proportions of potassium hydrosulfide with the dibromo acid **3** in the presence of copper. It was based on an early patent for synthesis of *o*-mercaptobenzoic acid.[21] We had avoided use of this deceptively simple route until information about **12** was available to permit its separation and identification. A principal complication which was foreseen was that equilibria of thiol moieties with potassium hydrosulfide would lead to metal thiolates of **12**, which could react with the aryl bromide to form bisaryl sulfides, oligomers, and polymers. In route III, the dibromo acid **3** gave a product which showed no Beilstein test and had an ir spectrum identical with that of **12** from route I. Tlc showed a series of spots, however, although the dominant one did have the R_f value of **12**. Iodine titration showed only 67% of the thiol content expected for **12**. Ethanol roughly separated fractions with iodine titers ranging from 60–90% of expectation for **12**. One fraction gave an elemental analysis consistent with **12**, had an iodine titer of 90%, and was confirmed as **12** by converting it to ester **19** (identical with **19** from route II). Route III thus does afford a one-step synthesis for dithiol **12** but, since it gives a grossly impure product, the longer routes are preferred.

Route III was even less promising for the monothiol **15** than for the dithiol **12**. Conditions identical with those used in the bis series (for **12** from **3**) converted the monobromo acid **7** to a product which showed only 55% of the thiol content expected for **15** (iodine titration). Tlc showed two spots, even after recrystallizations, suggesting the impracticability of purification.

Route IV.—In a procedure based on one of Campbell,[15] **3** gave two products, **11** and **14**. We at first thought it surprising that reduction to **14** occurred, when we had not observed reduction of the dibromo diester **17**; however, *o*-bromobenzoic acid is reduced by copper to benzoic acid although its ester is unaffected;[22a,23] in suitable instances the aryl halides themselves may act as hydrogen donors.[22b,23]

The dibenzyl sulfide (**11**) was separated from the monobenzyl one (**14**) by the sparing solubility of its salt in 10% KOH (the dipotassium salt of **11** will dissolve, however, in very dilute base). The structure of **11** was confirmed by converting it to **18** (47%). Attempts using aluminum bromide to cleave both benzyl groups from **11** to give **12** invariably led to mixtures containing nondebenzylated products, perhaps because the reaction mixture was heterogeneous; in route II (homogeneous reaction mixture), the ester **18** was cleaved smoothly to **19**. The mixture could not be purified, but mass spectrometry showed that acid **12** and acid **11** with one benzyl group remaining were present.

Attempts also were made to debenzylate the monosulfide **14** to **15** with sodium in liquid ammonia.[14] The **14** was readily soluble, but the product was difficult to purify. Aluminum bromide in toluene was equally unpromising, perhaps because of sparing solubility; again, intractable mixtures of **14** and **15** resulted. No pure dithiol **12** or monothiol **15** could be isolated by route IV.

Reactions of Thiols (Scheme II).—Uses made of the thiols are summarized in Scheme II. Of the bisdisulfides prepared, the most important to us was 2,5-bis(2-aminoethyldithio)terephthalic acid (**23**), the bis analog of **1**.

Although route III (*via* the hydrosulfide) gave impure **12**, there seemed a possibility that this **12** could be converted to **23**, which might be purified, so that route III would afford a two-step synthesis of **23**. Reaction of this impure **12** in 4 equiv of aqueous alkali with thiosulfonate **2a** did indeed give bisdisulfide **23** (33%); use of **12** with 4 equiv of alkali will be referred to as route V. This **23** dissolved in acid and base, failed to decolorize iodine, and gave a negative nitroprusside test; later, it proved to be identical with **23** obtained by other routes. Use of route III thus *can* give a two-step synthesis of **23** from **3**. This **23** may be sufficiently pure for some purposes, but since it contained a persistent impurity which precluded a satisfactory elemental analysis the two-step advantage may be dubious.

Because of the low yield, conditions were tried such as those which were successful for **1**,[2a] but with DMF for ethanol (in which **12** is sparingly soluble) and DABCO for neutralization; such use of **12** in DMF with 4 mol of DABCO will be referred to as route VI. To test route VI, *o*-mercaptobenzoic acid and the thiolsulfonate **2a** were stirred for 4 hr in DMF–H_2O; neutralization of the homogeneous mixture with DABCO gave **1** in 60% yield. With pure dithiol **12** from route I, route VI gave the bisdisulfide **23** (85%), which could be purified nicely through its hydrochloride.

We felt that with this purer dithiol **12** from route I, the conditions of route V might produce further improvement; the yield of **23** became quantitative when route V was used, but the gain in yield was offset since analytically pure **23** again could not be obtained. Route VI, with purification *via* the hydrochloride, thus seems to be the best choice.

The product from the reaction of dithiol **12** with thiolsulfonate **2a** can hardly be other than bisdisulfide **23**. It dissolves in both dilute acid and base (but not in water), and formol titration gave a neutralization equivalent of 211 (calcd, 190). Furthermore (Scheme II), a dihydrochloride precipitated (93%) during the reaction of **12** with **2a** identical with **27** prepared from **23** (mentioned below). The ir spectrum of **23** met expectation (and resembled that of **1**). Neither **23** nor its salts were sufficiently soluble in D_2O for nmr analysis. Efforts to obtain a mass spectrum of **23** or **27** resulted in thermal decomposition.

In the synthesis of the 4-carboxy analog (**24**) of disulfide **1** a new problem arose; the second carboxyl group was not neutralized by an amine moiety. The reaction of monothiol **15** with thiolsulfonate **2a**, essentially by route VI, gave **24** in 24% yield. In an improvement (route VII, minimum DMF), the yield was increased to 67%. Compound **24** had ir absorption consistent with both carboxyl and carboxylate functions.

(21) L. Cassella and Co., Ltd., German Patent 189,200 (1906); *Chem. Abstr.*, **2**, 607 (1908).

(22) (a) W. R. H. Hurtley, *J. Chem. Soc.*, 1870 (1929). (b) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev. (London)*, **19**, 110 (1965).

(23) We are indebted to Professor Joseph F. Bunnett of the University of California, Santa Cruz, for bringing the work of ref 22 to our attention.

Also prepared from dithiol **12** was an analog of **23** with *n*-decyl groups on the nitrogen atoms (**25**); **25** was desired for testing for the same reason as an earlier *n*-decyl analog of **1**.[2a] The chief synthetic problem was that the requisite thiolsulfonate (**2b**) is virtually insoluble in water and DMF. It was circumvented, in a modification of route VI, by dissolving **2b** in ethanol–methylene chloride (66% yield).

The hydrochlorides **27**, **28**, and **29** were obtained from the presumed zwitterionic structures **23**, **24**, and **25**, respectively, by treating aqueous slurries with hydrochloric acid (Scheme II). Dihydrochloride **27** was more soluble than its parent (**23**) and was purified by dissolution in methanol, filtration, and precipitation with ether. Hydrochloride **28** could be purified by recrystallization from ethanol. When **29** was heated in ethanol, however, **25** soon precipitated, and attempted dissolution in ethanol even without heating still resulted in **25**; **29** could not be purified as such.

The ester **30** of the key carboxy bisdisulfide **23**, of interest for comparison biologically with the ester of **1**,[2a] was also sought because its synthesis from both **23** and **19** would further confirm the structure of **23**. Acid **27** gave ester **30**. In the independent synthesis, **19** was treated with thiolsulfonate **2a**. For its isolation, **30** was converted to the free base, which was extracted with chloroform and then quickly reextracted into acid, because such bases usually are quite subject to disproportionation to the two symmetrical disulfides. Compound **30** was identical in ir and tlc behavior (one spot) with **30** obtained from **27**.

Since the dihydrochloride **27** had precipitated directly in the reaction of **12** with **2a**, the possibility was tested that **30** also might precipitate directly in the reaction of **19** with **2a** and thus provide a simpler preparation; **30** did indeed so precipitate, but only in 26% yield.

Since a number of dithiocarbamates are active as antiradiation drugs,[2,4] the bisdithiocarbamate **26** also was of interest. As Scheme II shows, dithiol **19** gave **26** (41% yield).

Evaluations are in progress at the Walter Reed Army Institute of Research, Washington, D. C., for antiradiation drug activity (thus far, **27** has shown LD_{50} > 450 mg/kg and inactivity at 75–150 mg/kg; *cf.* ref 2b for procedures) and also for inhibition of schistosomiasis. Tests for inhibition of *Histoplasma capsulatum in vitro* are being performed by Dr. Ilda McVeigh of the Department of General Biology, Vanderbilt University;[2d] thus far, **12** and **19** have proved inactive.

Experimental Section[25]

Starting Materials.—2,5-Dibromo-*p*-xylene[26] and 2-bromoterephthalic acid (**7**)[27] were purchased and also were prepared by the procedures cited in respective yields of 59% and 71%; 2,5-dihydroxyterephthalic acid (**4**, 97%),[9] diethyl 2,5-dihydroxyterephthalate (**5**, 57%),[10] diethyl 2,5-dibromoterephthalate (**17**, 83%),[28] benzyl disulfide (method I of ref 29), dimethyl 2-hydroxyterephthalate (**9**, 77%),[13] and dimethyl 2-bromoterephthalate (**20**, 94%)[13] were prepared by the procedures cited; properties agreed well with those reported. Sodium phenylmethanethiolate was freshly made by adding α-toluenethiol to a 1.0 molar proportion of NaOEt (from Na in absolute EtOH protected by a soda lime trap) and removing excess EtOH (a wash of Et_2O then removed any disulfide formed), and KSH was prepared by saturating an aqueous solution of KOH with H_2S, removing H_2O, and washing with EtOH and then Et_2O. The $AlBr_3$ was purified as described,[20] was broken up and stored over P_2O_5, and was weighed in a nitrogen-filled glove bag. Toluene used in cleavages with $AlBr_3$ was a technical grade dried by distillation from P_2O_5. The following were used as purchased: *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), diethylene glycol (Chromatoquality), Cu powder (150 mesh), *N*,*N*-dimethylcarbamyl, and thiocarbamoyl chlorides, 1,4-diazabicyclo[2.2.2]-octane (DABCO), and 2-bromo-*p*-xylene. Thiolsulfonate **2a** was prepared as before,[30] and thiolsulfonate **2b** was kindly provided by Dr. E. A. Steck of the Walter Reed Army Institute of Research.

2,5-Dibromoterephthalic Acid (3).—In a procedure based on one of Friedman, Fishel, and Shechter,[8] 2,5-dibromo-*p*-xylene (17.16 g, 65 mmol), sodium dichromate dihydrate (46.50 g, 156 mmol), and H_2O (186 ml) were sealed in a Magne-Drive autoclave and were heated at 250° for 5 hr. The mixture was filtered, and the chromic oxide was washed with H_2O until the filtrate was colorless. The filtrates were combined, treated with decolorizing carbon, filtered, and acidified with 6 *N* HCl to precipitate colorless **3**, yield 11.96 g (57%), mp 315–318° (lit.[31] mp ~320°); material of this quality was used. Recrystallization from glacial HOAc gave 7.69 g (37% overall), mp 317–318°.

Larger scale preparations were carried out by E. I. DuPont de Nemours and Co. through the kindness of Dr. R. G. Downing. Optimum conditions seemed to be with 0.9 mol of dichromate and 0.3 mol of dibromoxylene in 560 g of H_2O at a temperature of 230° for 10 hr (59–64% conversion of the 2,5-dibromo-*p*-xylene). At 280° for 5 hr, degradation occurred; our conditions reportedly gave somewhat lower yields and less pure product.

Two other methods gave **3** only in very low yield. The reaction of Br_2, water, and *p*-xylene (sealed tube, 180°, 2 hr)[7] gave **3** in 12% yield, mp 317–318°, and oxidation of 2,5-dibromo-*p*-xylene with $KMnO_4$ using the Morton high-speed stirring technique[32] gave **3** in 16% yield, mp 318–320°.

2-Hydroxyterephthalic Acid (8).—In method based on that for **4**,[9] disodium 2-bromoterephthalate (13.01 g, 45 mmol, prepared by neutralizing the acid **7** and removing water completely), sodium acetate (8.12 g, 99 mmol) and Cu powder (0.0572 g, 0.9 mg-atom) were placed in H_2O (206 ml) with a little phenolphthalein solution. The mixture then was heated at reflux for ~10 hr. It slowly became acidic, and 5% aqueous KOH was occasionally added dropwise to maintain *ca.* pH 8. During the last hour of reflux, the solution remained basic. The alkaline solution then was filtered and was acidified with 10% HCl until precipitation of **8** as white solid was complete, yield of **8**, 8.13 g (99%), mp 320–322° dec (lit.[33] mp >330°).

1,4-*O*,*O*-2,5-Bis(ethoxycarbonyl)phenylene Bis(*N*,*N*-dimethylthiocarbamate) (6) and 1-*O*-2,5-Bis(methoxycarbonyl)phenyl *N*,*N*-Dimethylthiocarbamate (10).—Diethyl 2,5-dihydroxytereph thalate (**5**, 0.51 g, 2 mmol), DABCO (1.35 g, 12 mmol), and *N*,*N*-dimethylthiocarbamoyl chloride (1.48 g, 12 mmol) were stirred in DMF (9 ml) for 30 min. White solid which precipitated was washed with H_2O to remove DMF and amounted to 0.755 g (88%) of **6**, mp 206–209°. Recrystallization from absolute EtOH gave colorless **6** with a constant mp of 210–211°: ir

(24) L. Field and J. D. Buckman, *J. Org. Chem.*, **33**, 3865 (1968).

(25) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were obtained using a Beckman Model IR-10 with KBr pellets; bands reported were of at least medium intensity unless w (weak) is indicated. Nmr spectra were obtained using a Varian Model A-60 spectrometer (TMS). Mass spectra were kindly determined by C. T. Wetter at 70 eV using the direct inlet system on an LKB Model 9000 instrument, which was obtained through NSF Science Development Program Grant GU-2057. Moist extracts were dried using anhydrous $MgSO_4$, and solvents then were evaporated under reduced pressure with a rotary evaporator. Tlc was done on polyamide (Brinkman MN-Polygram 66 10 12) using AcOH or on silica gel (Eastman Chromagram 6060) with benzene, CH_2Cl_2, 95% EtOH, or 95% EtOH–H_2O–NH_4OH (25:3:4), with location of spots by a uv lamp or by I_2 vapor.

(26) P. Ruggli and F. Brandt, *Helv. Chim. Acta*, **27**, 274 (1944).

(27) S-H. Yen, *Chlorine Alkali News*, **11**, 44 (1953); *Chem. Abstr.*, **49**, 7523 (1955).

(28) A. S. Wheeler and E. W. Constable, *J. Amer. Chem. Soc.*, **45**, 1999 (1923).

(29) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *ibid.*, **73**, 3627 (1951).

(30) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *ibid.*, **83**, 4414 (1961).

(31) A. Claus and C. Wimmel, *Ber.*, **13**, 902 (1880).

(32) A. A. Morton, B. Darling, and J. Davidson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 734 (1942).

(33) H. Fischli, *Ber.*, **12**, 615 (1879).

(KBr) 1720, 1545 [C(S)N],[34] 1385, 1255, 1180 [-C(S)-],[34] and 870 (w) cm^{-1}; nmr ($DCCl_3$) δ 1.33 (t, 6), 3.43 (s, 6), 3.48 (s, 6), 4.3 (q, 4), and 7.78 (s, 2).

Anal. Calcd for $C_{18}H_{24}N_2O_6S_2$: C, 50.45; H, 5.65; N, 6.54; S, 14.96. Found: C, 50.35; H, 5.68; N, 6.64; S, 14.93.

When DABCO was added to a solution of 2,5-dihydroxyterephthalic acid (4) in DMF, a solid precipitated (probably the salt of 4). Addition of *N,N*-dimethylthiocarbamoyl chloride to this mixture, followed by heating at 70° for 5 hr, failed to give the acid of 6.

Much the same procedure used for 6 converted the monohydroxy diester 9 to its thiocarbamate 10: dimethyl 2-hydroxyterephthalate (9, 2.48 g, 12 mmol), DABCO (4.04 g, 36 mmol), and *N,N*-dimethylthiocarbamoyl chloride (4.44 g, 36 mmol) were stirred in DMF (18 ml) at ~25° for 5 hr. The homogeneous mixture then was poured into H_2O (72 ml) to precipitate yellow 10, yield 3.30 g (94%), mp 80–105°. Two recrystallizations from MeOH gave colorless 10: yield 2.03 g (58%); constant mp 113–114°; ir (KBr) 1720, 1540 [C(S)N],[34] 1400, 1280, 1240 [-C(S)-],[34] 1110, 890 (w), and 820 (w) cm^{-1}; nmr ($DCCl_3$) δ 3.42 (s, 3), 3.47 (s, 3), 3.85 (s, 3), 3.93 (s, 3), 7.78 (m, 1), and 8.0 (m, 2).

Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71; S, 10.78. Found: C, 52.92; H, 5.29; N, 4.80; S, 10.66.

1,4-*S*,*S*-2,5-Bis(ethoxycarbonyl)phenylene Bis(*N,N*-dimethylthiocarbamate) (13) and 1-*S*-2,5-Bis(methoxycarbonyl)phenyl *N,N*-Dimethylthiocarbamate (16).[35] A. *S,S*-Bisthiocarbamate (13) from *O,O*-Bisthiocarbamate 6 (Route I).—Compound 6 (9.25 g, 22 mmol) was heated neat at 230° for 30 min (Wood's metal). Cooling gave 9.00 g (97%) of 13, mp 107–140°. One recrystallization from absolute EtOH gave 7.07 g (76%), mp 135–145°, and further recrystallization gave white 13 with a constant mp of 143–146° (on a large scale, 6 and 13 were less soluble in EtOH and were recrystallized from benzene): ir (KBr) 1710, 1660 [-SC(O)NR_2],[36] 1360, 1330, 1270 (w), 1220, 1130, 1095, 895 (w), and 860 (w) cm^{-1}; nmr ($DCCl_3$) δ 1.35 (t, 6), 3.08 (s, 12), 4.33 (q, 4), and 8.10 (s, 2).

Anal. Calcd for $C_{18}H_{24}N_2O_6S_2$: C, 50.45; H, 5.65; N, 6.54; S, 14.96. Found: C, 50.44; H, 5.74; N, 6.57; S, 14.80.

When the *O,O*-bisthiocarbamate (6) was heated at 280° for 30 min, the melt darkened; tar resulted. At 230° decomposition seemed slight.

B. The *S,S*-Bisthiocarbamate 13 from the Dimercapto Diester 19.—DABCO (0.335 g, 3 mmol) and 19 (0.143 g, 0.5 mmol) were dissolved in DMF (8 ml). A red solution and a precipitate quickly resulted. *N,N*-Dimethylcarbamyl chloride (~0.5 ml) was added rapidly with stirring. The solution became colorless, and white solid precipitated. Stirring was continued for 1 hr, and the solid then was collected by filtration. This solid, soluble in water, evidently was DABCO·HCl. Addition of H_2O (30 ml) to the filtrate and cooling gave 13 as white solid, yield 0.147 g (69%), mp 130–137°. One recrystallization from absolute EtOH gave 0.106 g (50%) of 13, mp 142–146°, identical in its ir spectrum with the 13 from A.

C. The *S*-Monothiocarbamate 16 from the *O*-Monothiocarbamate 10 (Route I).—In a procedure much like that of A, 10 (1.45 g, 4.9 mmol) was heated neat at 230° for 0.5 hr. An oil resulted (even after 5 days), but it solidified when rubbed under hexane, yield of 16 0.70 g (48%), mp 65–68°. This 16 was recrystallized from benzene, then twice from MeOH–H_2O, to give colorless 16 having a constant mp 67–68°. Analysis indicated the presence still of a persistent impurity (Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71; S, 10.78. Found: C, 53.34; H, 5.05; N, 4.78; S, 11.63), so identification was made by the spectra: ir (KBr) 1730, 1665 [-SC(O)NR_2],[36] 1440, 1370, 1300, 1260, 1100, 1060, 870 (w), and 820 (w) cm^{-1}; nmr ($DCCl_3$) δ 3.05 (s, 6), 3.88 (s, 3), 3.92 (s, 3), and 8.08 (m, 3); mass spectrum *m/e* (rel intensity) 297 (31), 266 (18), 225 (13), 210 (8), 194 (7), 178 (6), 166 (3), 163 (4), 135 (12), 108 (5), 107 (6), 72 (100), 63 (12), and 42 (11).

Lower temperatures than 230° resulted in incomplete rearrangement and higher ones in unnecessary decomposition.

2,5-Dimercaptoterephthalic Acid (12) and 2-Mercaptoterephthalic Acid (15). A. Dimercapto Acid 12 from the *S,S*-Bisthiocarbamate 13 (Route I).—A 1.74 *N* solution (23.4 ml) of KOH in diethylene glycol was heated to 120–130°; 2.50 g (5.8 mmol) of 13 was added in one portion. The solution was heated under N_2 at 120–130° for 20 min; solid appeared. The solution was cooled and diluted with H_2O (234 ml), thus dissolving the solid. The solution was acidified with 10% HCl until precipitation of yellow solid was complete, yield of 12 1.35 g (100%), mp >350°. Titration with I_2 showed 90% of expectation for 2 SH groups; the ir spectrum showed this 12 to be of good quality and, owing to large losses on recrystallization, it was used as such for subsequent reactions. Two recrystallizations from glacial HOAc gave 0.146 g of deep yellow 12 (11%): mp >350°; ir (KBr) 3300–2500, 1680, 1480, 1410, 1300, 1250, 1090, 900, and 785 cm^{-1}; nmr as described in the discussion; mass spectrum *m/e* (rel intensity) 230 (32), 212 (45), 194 (100), 166 (25), 138 (15), and 69 (22); uv max (95% C_2H_5OH) 276 nm (ϵ 11,110), 375 (2722), and 435–470 (560–110, hence a yellow color);[37] tlc in HOAc on polyamide gave only one spot, R_f 0.39.

Anal. Calcd for $C_8H_6O_4S_2$: C, 41.73; H, 2.63; S, 27.85. Found: C, 41.86; H, 2.77; S, 27.47.

B. Dimercapto Acid 12 from Diester 19 (Route II).—Much as in A, 19 (1.43 g, 5 mmol) was placed in 17.82 ml of a 1.40 *N* solution of KOH in diethylene glycol at 120–130°. The solution was heated under N_2 (20 min) and then was diluted with H_2O (85 ml). Acidification with 10% HCl to pH 1 precipitated 12 of good quality (ir), yield 1.24 g (108%), mp >350°. Two recrystallizations from glacial HOAc gave 0.129 g (11%) of deep yellow 12, mp >350°; the ir spectrum and tlc in HOAc on polyamide were identical with those of 12 from A.

Anal. Calcd for $C_8H_6O_4S_2$: C, 41.73; H, 2.63; S, 27.85. Found: C, 41.97; H, 2.75; S, 27.87.

In two previous attempts to prepare diacid 12 from diester 19 impurity observed was believed (tlc) to be the monoester.

C. Dimercapto Acid 12 from Dibromo Acid 3 (Route III).—In a procedure based on one for *o*-mercaptobenzoic acid,[21] KSH (42.52 g, 589 mmol), Cu powder (0.609 g, 9.58 mg-atoms), and 3 (23.84 g, 73.6 mmol) were placed in diethylene glycol (136 ml); N_2 was bubbled through the mixture for 30 min to purge air. The stream of N_2 then was stopped, and the mixture was heated at 175° for 3 hr. It then was cooled. Water (1360 ml) was added, and the solution was treated with decolorizing carbon and filtered. The filtrate, acidified to pH 1, gave a yellow compound 12, 19.09 g (113%), mp >350°. The Beilstein test (hot copper wire) was negative (strongly positive for 3). Extraction of the crude 12 with 95% EtOH in a Soxhlet extractor gave seven fractions. Fraction 7, recrystallized twice from glacial HOAc, gave a deep yellow compound 12, mp >350°, identical in its ir spectrum and tlc behavior with 12 from A, iodine titer 90% of expectation for 12.

Anal. Calcd for $C_8H_6O_4S_2$: C, 41.73; H, 2.63; S, 27.85. Found: C, 42.10; H, 2.45; S, 27.80.

This procedure is not the best for the dimercapto acid 12 because the 12 is impure; the seven fractions varied in iodine titer from 60–90%. Attempts to separate pure 12 using benzylisothiuronium chloride or DABCO failed.

D. Monomercapto Acid 15 from Monomercapto Ester 22 (Route II).—In a procedure much like that in B, 22 (7.64 g, 33.8 mmol, somewhat crude as reported later for 22) was placed in 80 ml of a 1.40 *N* solution of KOH in diethylene glycol at 120–130°. The solution was heated as before, H_2O (400 ml) was added, and the solution was acidified with 10% HCl to pH 1 to precipitate 15 as cream-colored solid: yield 3.85 g (57%); mp >320°. This 15 by ir was of good purity and because of large losses on recrystallization was used for subsequent reactions; 0.734 g was recrystallized twice from glacial HOAc to give 0.188 g (26% yield) of a pale yellow compound 15: mp >320°; tlc on silica gel in 95% EtOH–H_2O–NH_4OH (25:3:4) gave one spot, R_f 0.27; ir (KBr) 3200–2300, 1675, 1480, 1410, 1260, 890, 775, and 745 cm^{-1}; mass spectrum *m/e* (rel intensity) 198 (20), 180 (100), 152 (8), 135 (36), 69 (8), and 45 (7).

Anal. Calcd for $C_8H_6O_4S$: C, 48.48; H, 3.05; S, 16.18. Found: C, 48.59; H, 3.12; S, 16.30.

Diethyl 2,5-Bis(benzylthio)terephthalate (18) and Dimethyl 2-(Benzylthio)terephthalate (21). A. The Bissulfide 18 from the Dibromo Ester 17 (Route II).—A mixture of sodium phenylmethanethiolate (6.43 g, 44 mmol) and 17 (8.36 g, 22 mmol) in DMA (83 ml) was heated at 75° for 24 hr. DMA was removed

(34) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 350.

(35) These procedures were based on the method of Newman and Karnes.[11]

(36) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 255.

(37) C. R. Noller, "Chemistry of Organic Compounds," W. B. Saunders, Philadelphia, Pa., 1965, p 737.

by vacuum distillation until a thick slurry remained. Benzene (100 ml) and H_2O (100 ml) were added, and the H_2O layer was extracted repeatedly with benzene until an extract was colorless. The benzene extracts were combined, dried, and concentrated to give **18**, yield 10.35 g (100%), mp 75–101°. Compound **18**, recrystallized from absolute EtOH, gave 5.17 g (50%), mp 137–140°. Further recrystallization gave yellow **18** with constant mp 140–142°; ir (KBr) 1710, 1460, 1370, 1300, 1225, 1075, 885 (w), 775, 710, and 690 cm^{-1}; nmr ($DCCl_3$) δ 1.35 (t, 6), 4.13 (s, 4), 4.35 (q, 4), 7.32 (m, 10), and 7.87 (s, 2); mass spectrum *m/e* (rel intenstiy) 468 (8), 467 (26), 92 (11), 91 (100), and 65 (13).

Anal. Calcd for $C_{28}H_{26}O_4S_2$: C, 66.92; H, 5.62; S, 13.74. Found: C, 66.93; H, 5.73; S, 13.58.

The ester was used instead of the sodium salt of acid **3** because the salt led to a solid that gave a positive Beilstein test and a negative sulfur test (sodium fusion) indicating little reaction. Reaction under the conditions of A of the known diethyl 2,5-dichloroterephthalate gave **18** in 29–46% yield, mp 137–140°, identical with that from **17** (ir).

B. The Diester 18 from the Bis(benzylthio) Acid 11.—A mixture of concentrated H_2SO_4 (1 ml) and crude **11** (41.0 mg, 0.1 mmol) in absolute EtOH (20 ml) was heated at reflux for 12 hr. The solution was neutralized with a KOEt solution to pH 7, and the EtOH was evaporated. The residue was extracted with Et_2O, and the solution was washed with H_2O. The Et_2O solution was dried and evaporated to give **18** as yellow solid, 22.0 mg (47%). One recrystallization from absolute EtOH gave 8.0 mg (17% overall) of **18**, mp 133.5–135°, identical in ir spectrum with the **18** from **17** and sodium phenylmethanethiolate.

C. The Monosulfide 21 from the Monobromo Ester 20 (Route II).—Much as in A, the bromo ester **20** (3.55 g, 13 mmol) and sodium phenylmethanethiolate (1.90 g, 13 mmol) in DMA (48 ml) were heated at 75° for 24 hr. DMA was removed, benzene and H_2O were added, and benzene extracts then were combined, dried, and evaporated to give 1.40 g of **21** (34%). Two recrystallizations from MeOH gave 0.415 g of colorless **21** (10% from **20**): constant mp 94–96°; ir (KBr) 1710, 1435, 1250, 1060, 850 (w), 810 (w), 740, 710, and 690 cm^{-1}; nmr ($DCCl_3$) δ 3.93 (s, 6), 4.22 (s, 2), 7.5–7.2 (m, 5), 7.84 (m, 1), 7.95 (m, 1), and 8.1 (m, 1); mass spectrum *m/e* (rel intensity) 316 (18), 285 (6), 284 (11), 225 (16), 92 (8), 91 (100), and 65 (9); tlc in benzene on silica gel gave a single spot, R_f 0.26.

Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10; S, 10.13. Found: C, 64.64; H, 5.19; S, 9.97.

Diethyl 2,5-Dimercaptoterephthalate (19) and Dimethyl 2-Mercaptoterephthalate (22). A. The Dimercapto Diester 19 from the Bisbenzyl Sulfide 18 (Route II).—A solution of $AlBr_3$ (0.59 g, 2.2 mmol) in dry toluene (10 ml) was placed in a 25-ml three-necked flask equipped with a drying tube ($CaCl_2$). Addition of **18** (0.467 g, 1 mmol) immediately led to a red precipitate. The mixture was heated at 60° for 6 hr with stirring. Water (1 ml) then was added to the cooled mixture during 30 min with stirring. Then more H_2O (1.5 ml) was added at one time, and the mixture was stirred for 20 min. The mixture was extracted with 5% aqueous KOH, and the basic solution was filtered into concentrated HCl, yield of **19** which precipitated 0.217 g (76%), mp 133–135°. Recrystallization from absolute EtOH gave yellow **19** having a constant mp 131–133°: ir (KBr) 2500, 1710, 1460, 1360, 1290, 1235, 1130, 1080, 1010, 890 (w), 860 (w), and 770 cm^{-1}; nmr [$D_3CC(O)CD_3$] δ 1.40 (t, 6), 4.40 (q, 4), 5.03 (s, 2), and 8.06 (s, 2); mass spectrum *m/e* (rel intensity) 286 (33), 240 (33), 194 (100), 166 (15), 138 (11), 95 (22), and 69 (19); titration with I_2, 99% for 2 SH moieties; uv max (95% C_2H_5OH) 276 (ϵ 12,110), 303 (1556), 378 (3110), and 435–450 nm (220–110, hence a yellow color).[37]

Anal. Calcd for $C_{12}H_{14}O_4S_2$: C, 50.33; H, 4.93; S, 22.39. Found: C, 50.17; H, 4.84; S, 22.50.

The toluene in the above reaction must be dry; otherwise hydrolysis of the ester groups leads to a mixture (containing acids and *S*-benzyl compounds) that is almost impossible to separate.

Bisbenzyl sulfide **18** (1.00 g, 2.14 mmol) also was cleaved with Na using liquid NH_3 (250 ml), which gave a heterogeneous mixture. Sodium (0.9 g, 39 mg-atoms) was added until the solution became blue and the blue color persisted for 30 min; NH_4Cl (0.79 g, 15 mmol) then was added. After evaporation of the NH_3, addition of H_2O, and acidification to pH 1, solid precipitated; extraction into Et_2O and evaporation gave 0.527 g (86%) of **19** as yellow semisolid; the ir (neat) and nmr spectra were essentially identical with those (ir, KBr) of the **19** formed with $AlBr_3$; addition of D_2O caused a nmr peak at δ 5.07 to disappear; **19** decolorized I_2.

B. The Dimercapto Diester 19 from the Diacid 12.—Concentrated H_2SO_4 (0.4 ml) and **12** (0.23 g, 1 mmol, from route III) were heated under reflux in absolute EtOH (8 ml) for 4 hr. The solution was cooled, neutralized with KOEt solution, and K_2SO_4 was separated by filtration. Evaporation of the filtrate gave 0.220 g (77%) of yellow **19**, mp 62–120°. One recrystallization from absolute EtOH gave 0.100 g (35%), mp 133–135° (ir spectrum identical with that of **19** obtained under A).

C. Monomercapto Diester 22 from Monobenzyl Sulfide 21 (Route II).—In essentially the procedure of A, **21** (0.95 g, 3 mmol) was heated in dry toluene containing $AlBr_3$ (1.76 g, 6.6 mmol) at 60° for 3 hr, the mixture was cooled, and H_2O (3 ml) was added (30 min) followed by 4.5 ml more of H_2O in one portion. The mixture was stirred for 20 min, Et_2O was added to dissolve solid, and the solution was extracted as before with 5% aqueous KOH. The basic extract was treated with decolorizing carbon and filtered, and the filtrate was acidified with 10% HCl to pH 1 to precipitate white **22**, yield 0.655 g (97%), mp 202–212°. The ir spectrum of this **22** indicated presence of carboxyl groups; since recrystallization from MeOH failed to give pure **22**, the mixture therefore was saponified directly to acid **15**.

2,5-Bis(benzylthio)terephthalic Acid (11) and 2-(Benzylthio)-terephthalic Acid (14) (Route IV).—Acid **3** (25.92 g, 80 mmol), benzyl disulfide (19.71 g, 80 mmol), and Cu powder (10.17 g, 160 mg-atoms) in DMA (480 ml) were heated to 70–75°. Solid appeared and the solution became green. The solution was heated at 70–75° with vigorous stirring for 2 hr and then at reflux (~165°) for 10 hr. DMA was removed by vacuum distillation until a thick slurry remained. The slurry was made basic with 10% aqueous NaOH. Solid was removed by filtration, and the filtrate was acidified with 10% HCl to pH 1; 35.58 g of a yellow mixture of **11** and **14** precipitated.

This yellow solid was stirred with 10% aqueous KOH to leave undissolved 6.11 g of sparingly soluble potassium 2,5-bis(benzylthio)terepthhalate. This white salt of **11** was collected by filtration and dried. When it then was stirred with 10% HCl, yellow solid precipitated: yield of **11** 4.03 g (12%); mp 309–316° dec; ir (KBr) 1690, 1250, 1230, 715, and 690 cm^{-1}; tlc in HOAc on polyamide showed 3 spots, and no purification was attempted. The structure of **11** was confirmed by preparing the bisbenzylthio ester **18** (*vide supra*).

The basic solution (in which the potassium salt of **11** had been sparingly soluble) was acidified to precipitate a second solid. This solid, collected by filtration and dried, gave 8.55 g (37%) of yellow **14**, mp ~246° dec (sublimation). The **14** was recrystallized from *tert*-BuOH–H_2O to a constant ir spectrum: (KBr) 1690, 1480, 1410, 1290, 1250, 780, 745, 710, and 690 cm^{-1}.

Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.49; H, 4.19; S, 11.12. Found: C, 62.23; H, 4.08; S, 11.14.

2,5-Bis(2-aminoethyldithio)terephthalic Acid (23) and 2-(2-Aminoethyldithio)terephthalic Acid (24). A. Bisdisulfide 23 from the Dimercapto Acid 12 (Route VI).—A solution of **12** from route I (0.921 g, 4 mmol) in DMF (38 ml) was added with stirring to a solution of thiolsulfonate **2a** (2.06 g, 8 mmol) in 5.03 ml of H_2O–DMF (7:1). Yellow solid began to precipitate after 5 min. The mixture was stirred for 5.5 hr and then was neutralized at 0° with a cold solution of DABCO (1.79 g, 16 mmol) in H_2O (6.3 ml). The yellow solid immediately became white. Filtration separated 1.29 g (85%) of **23**, mp 243–245° dec. Purification was effected by dissolution in 0.258 *N* HCl, filtration, and neutralization with 0.250 *N* NaOH to pH 7. Three repetitions gave white **23** having a constant mp 251.5–252.5° dec: ir (KBr) 3400, 3100–2500, 1630, 1560, 1445, 1370, and 810 cm^{-1}; too sparingly soluble for an nmr spectrum.

Anal. Calcd for $C_{12}H_{16}N_2O_4S_4$: C, 37.88; H, 4.24; N, 7.36; S, 33.70; neut equiv, 190. Found: C, 37.64; H, 4.32; N, 7.17; S, 33.55; neut equiv (formol), 211.[38]

Use of the tetrasodium salt of **12** was less satisfactory (route V). Thus, when **12** (from route I, 0.921 g, 4 mmol) was dissolved in a solution of NaOH (0.64 g, 16 mmol) in H_2O (1.28 ml) and added to a solution of thiolsulfonate **2a** (2.06 g, 8 mmol) in H_2O (5 ml), white solid precipitated. Filtration separated 1.57 g (103%) of **23**, mp 241–243° dec, which, twice purified by dis-

(38) In the formol titration (*cf.* ref 2a), a 37% formaldehyde solution was neutralized (phenolphthalein end point) and added to an aqueous slurry of **23**. This mixture then was neutralized (phenolphthalein end point).

solution in HCl, filtration, and neutralization as before, gave white **23** with a constant mp of 250–251° dec. The ir spectrum was identical with that of the **23** from route VI, but a satisfactory analysis could not be obtained (Found: C, 36.29; H, 4.42). When an nmr spectrum of this **23** was attempted in D_2O–H_2SO_4, yellow solid appeared immediately; the ir spectrum suggested the solid was a salt of **23** with H_2SO_4 since there was a strong broad band at 1075 cm^{-1} (**23**·HCl also was too sparingly soluble to give an nmr spectrum; *vide infra*).

Variations of route V were less promising. Use of crude **12**, prepared by the one-step reaction of KSH with acid **3** (route III), with thiolsulfonate **2a** gave the desired **23** but in yields of 25–33%.

B. The Monodisulfide 24 from the Monomercapto Acid 15 (Route VII).—A solution of **15** (0.198 g, 1 mmol) in 95% EtOH (3.68 ml), with barely enough DMF to effect solution at boiling, was added to a solution of thiolsulfonate **2a** (0.257 g, 1 mmol) in 0.63 ml of H_2O–95% EtOH (7:1). The mixture was stirred for 4 hr and cooled at 5°, and a cooled solution of DABCO (0.224 g, 2 mmol) in H_2O (0.8 ml) was added. In ~20 min a white precipitate began to appear. The mixture was stirred for 1 hr and then cooled overnight. The solid was collected and washed with EtOH and Et_2O, yield of a white compound **24** 0.183 g (67%), mp 265–267° dec. Two recrystallizations from H_2O gave 0.0424 g (16%) of a white compound **24** with a constant mp 263–264° dec: ir (KBr) 1690, 1620, 1510, 1410, 1370, 1240, 1130, 1030, 940, 875, 780, and 760 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_4S_2$: C, 43.95; H, 4.04; N, 5.13; S, 23.47; neut equiv, 137. Found: C, 44.13; H, 4.16; N, 4.99; S, 23.10; neut equiv (formol), 130.[38]

The use of DMF–H_2O, essentially route VI, gave disulfide **24** in 24% yield, ir similar but not identical with that of **24** from route VII; loss through excessive solubility of **24** apparently occurred, and the ir suggested less satisfactory **24**.

2,5-Bis(2-aminoethyldithio)terephthalic Acid Dihydrochloride (27) and 2-(2-Aminoethyldithio)terephthalic Acid Hydrochloride (28).—Concentrated HCl (0.5 ml) was added to a suspension of **23** (0.250 g, 0.66 mmol) in H_2O (3 ml) to give a yellow solid, yield 0.218 g (73%), mp 283–286°. This, after two recrystallizations from MeOH by addition of Et_2O, gave the yellow compound **27**: yield 0.091 g (30%), having a constant mp 280–281° dec; ir (KBr) 3200-2500, 1690, 1460, 1410, 1310, 1250, 1080, 890, and 790 cm^{-1}; **27** was too sparingly soluble for a nmr spectrum in D_2O.

Anal. Calcd for $C_{12}H_{18}Cl_2N_2O_4S_4$: C, 31.78; H, 4.00; Cl, 15.64; N, 6.18; S, 28.29. Found: C, 32.02; H, 4.17; Cl, 15.43; N, 6.01; S, 28.01.

In the preparation of bisdisulfide **23** by route VI, the yellow solid which precipitated before the neutralization with DABCO proved to be the dihydrochloride **27** (mp 278–281°, 93% yield); the ir spectra of the two samples of **27** were identical.

Disulfide **24** (0.300 g, 1.1 mmol) was placed in H_2O (5 ml) and and concentrated HCl (1 ml) was added. Part of the hydrochloride dissolved, so the solution was evaporated to leave 0.294 g (86%) of **28**, mp >320°. Two recrystallizations from absolute EtOH gave 0.0697 g (20%) of white **28**, mp >320°: ir (KBr) 3200–2500, 1675, 1470, 1400, 1250, 920, 880, 780, and 740 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}ClNO_4S_2$: C, 38.77; H, 3.90; N, 4.52; S, 20.70. Found: C, 39.14; H, 3.98; N, 4.82; S, 21.20.

2,5-Bis(2-*n*-decylaminoethyldithio)terephthalic Acid (25).—A solution of dithiol **12** (0.461 g, 2 mmol) in DMF (3.76 ml) was added to one of thiolsulfonate **2b** (2.15 g, 4 mmol) in 80 ml of 1:1 CH_2Cl_2–EtOH (this solution of **2b** was prepared at the boiling point and then cooled to ~25°). The mixture was stirred for 4 hr, during which it remained homogeneous, after which DABCO (0.897 g, 8 mmol) in DMF (7 ml) was added (essentially route VI). A copious amount of white solid precipitated immediately and did not increase significantly upon storage at 0° overnight. The solid, washed with EtOH and Et_2O, amounted to 0.87 g (66%) of **25**, mp 202–205° dec. The **25** was purified by stirring 0.205 g with 14 ml of 0.0966 *N* aqueous HCl for 20 min. The solid, then presumably largely **25**·HCl, was virtually insoluble in H_2O and was extracted, by shaking, into a solution of DMF–CH_2Cl_2–EtOH (1:1:1). This solution then was neutralized with one of DABCO (0.067 g, 0.6 mmol) in absolute EtOH (7 ml) to pH 7 to give **25**, 0.139 g (68% recovery), mp 211-213° dec. Repetition of the procedure gave 0.095 g (46% recovery of a white powdery compound **25**: mp 212–214° dec; ir (KBr) similar to **23** but simpler, 3400 (w), 2920, 2850, 1610, 1560, 1450 (doublet), 1360, 815, 795, and 725 (br, w) cm^{-1}. The **25** was too sparingly soluble for nmr or neutral equivalent (formal) studies.

Anal. Calcd for $C_{32}H_{56}N_2O_4S_4$: C, 58.14; H, 8.54; N, 4.24. Found: C, 58.44; H, 8.97; N, 4.25.

Diethyl 2,5-Bis(2-aminoethyldithio)terephthalate Dihydrochloride (30). A. Ester 30 from Bisdisulfide 27.—Hydrochloride **27** (0.628 g, 1.4 mmol) and *p*-toluenesulfonic acid·H_2O (12.43 g, 65 mmol) were heated in absolute EtOH (314 ml) at reflux for 14 hr. The EtOH was evaporated to a volume of ~25 ml, and H_2O (25 ml) was added. The solution was made basic (pH 9) with 5% aqueous KOH and extracted with $CHCl_3$. The $CHCl_3$ extracts were combined and rapidly extracted with 0.0966 *N* HCl. The acid extracts were combined, evaporated to dryness, and the residue was rubbed with acetone to give 0.648 g (88%) of **30**·H_2O, mp 235–240° dec. This procedure was repeated to give white **30**·H_2O, yield 0.212 g (29%), mp 268–270° dec. Two recrystallizations from absolute EtOH gave white **30**·H_2O: yield 0.064 g (9%) with a constant mp 267–268°; ir (KBr) 3200–2500, 1710, 1450, 1290, 1230, and 1070 cm^{-1}. A satisfactory analysis could not be obtained, evidently because of a persistent impurity associated with disproportionation, complicated by uncertain solvation (Found: C, 38.52; H, 4.88; S, 22.50), but **30** was identical with that from B (*vide infra*) in its ir spectrum and in its tlc behavior (identical single spots when both samples and a mixture were done concurrently).

In other efforts to convert **27** to **30**, **27** (5.9 mmol) was heated under reflux with PCl_5 (17.6 mmol) in AcCl (64 ml) for 24 hr, but cooling and filtration gave only **27** (91% recovery, ir spectrum identical with that of pure **27**). When **27** (0.800 g, 1.8 mmol) was heated in 1200 ml of boiling absolute EtOH with vigorous stirring for 6 hr, removal of excess **27** showed that 0.500 g (1.1 mmol) of **27** had dissolved; the solution was refluxed while HCl was bubbled in during 24 hr (tlc then showed that ester **30** might be present), the EtOH was evaporated, and residual solid was dissolved in water, basified, and extracted with $CHCl_3$; the $CHCl_3$ solution was extracted with 0.0966 *N* HCl, and the acid extract was evaporated to give 0.0288 g (5%) of **30**·H_2O, mp 248–252° dec. Recrystallization from absolute EtOH gave 0.010 g (2%) of **30**·H_2O, mp 265–268°, which was identical (ir) with **30** prepared using *p*-toluenesulfonic acid.

B. The Ester 30 from Dithiol 19.—A solution of **19** (0.2214 g, 0.77 mmol) in 5.6 ml of 0.270 *N* NaOH was added dropwise during 30 min to a stirred solution of **2a** (0.792 g, 3.08 mmol) in H_2O (10 ml). The solution was cooled overnight at 5°, and 5% aqueous KOH then was added to pH 11. The alkaline solution was extracted twice with $CHCl_3$, and the $CHCl_3$ extract was acidified by shaking with 10% HCl to pH 1. Evaporation of the aqueous layer to dryness gave 0.157 g (39%) of **30**·H_2O, mp 263–265° dec. Recrystallization from absolute EtOH gave 0.0834 g (20%) of the white compound **30**·H_2O: mp 267–268° dec; tlc (silica gel, 95% EtOH) showed only one spot (R_f 0.12); ir (KBr) 3200–2500, 1710, 1450, 1290, 1230, and 1070 cm^{-1}; too sparingly soluble for a nmr spectrum.

Anal. Calcd for $C_{16}H_{28}Cl_2N_2O_4S_4 \cdot H_2O$: C, 36.43; H, 5.35; S, 24.31; H_2O, 3.41. Found: C, 36.26; H, 5.41; H_2O, 1.72.[39]

1,4-*S*,*S*-2,5-Bis(ethoxycarbonyl)phenylene Bis(*N*,*N*-dimethyldithiocarbamate) (26).—*N*,*N*-Dimethylthiocarbamoyl chloride (23.73 g, 192 mmol), DABCO (21.54 g, 192 mmol), and **19** (9.26 g, 32 mmol) were stirred in DMF (144 ml) at ~25° for 2 hr. Solid which precipitated was collected, washed with H_2O, and dried, yield of **26** 4.17 g (28%), mp 197–202°. Addition of H_2O to the filtrate precipitated more **26** (12.53 g, 84%). The solids were combined and recrystallized from CH_3NO_2–EtOH to give 6.19 g (41%) of **26** as fine yellow needles, mp 197–202°. Three recrystallizations from benzene and one from benzene–EtOH gave white **26** with a constant mp 215–217°; ir (KBr) 1725, 1640, 1500, 1370, 1240, 1130, 1070, 970, and 850 cm^{-1}; nmr ($DCCl_3$) δ 1.37 (t, 6), 3.55 (s, 12), 4.32 (q, 4), and 8.17 (s, 2).

(39) The **30**·H_2O was dried for 6 hr at 100° (0.5 mm) before submission for analysis (presumably with partial loss of H_2O), after which the analyses reported for H_2O was based on further drying for 24 hr at 100° (0.5 mm); the analysis after the latter drying was unsatisfactory for anhydrous **30**, probably because of decomposition during the vigorous drying [Calcd for (anhydrous) $C_{16}H_{28}Cl_2N_2O_4S_4$: C, 37.71; H, 5.14; S, 25.17. Found: C, 36.43; H, 5.09]. It seems clear that **30** is a hydrate, but whether or not it is a monohydrate is unclear.

Anal. Calcd for $C_{18}H_{24}N_2O_4S_4$: C, 46.93; H, 5.25; N, 6.08; S, 27.84. Found: C, 47.23; H, 5.40; N, 6.15; S, 27.79.

Registry No.—**6**, 25906-63-2; **10**, 25906-64-3; **11**, 25906-65-4; **12**, 25906-66-5; **13**, 25906-67-6; **14**, 25906-68-7; **15**, 25906-69-8; **16**, 25906-70-1; **18**, 25906-71-2; **19**, 25906-72-3; **21**, 25906-73-4; **22**, 25906-74-5; **23**, 25906-75-6; **24**, 25906-76-7; **25**, 25906-77-8; **26**, 25902-98-1; **27**, 25902-99-2; **28**, 25957-59-9; **30**, 25903-00-8.

The Stereochemistry of Oxidation at Sulfur. Oxidation of 2-Methylthiolane[1,2]

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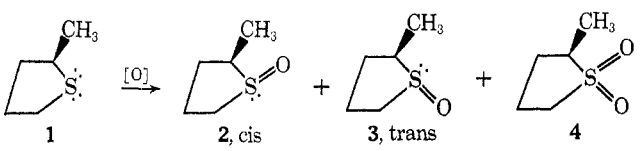
Pure samples of the diastereomeric 2-methylthiolane 1-oxides were isolated and characterized by chromatographic retention time and nmr spectroscopy. The cis isomer exhibits the shorter retention times on chromatography. The methyl resonance of the trans isomer shows the greater benzene-induced shift. The stereochemistry of oxidation of 2-methylthiolane by a variety of reagents is recorded.

Oxidation of sulfides is likely to remain the foremost method for the preparation of sulfoxides. The availability of stereochemical data on this transformation is useful from both mechanistic and synthetic standpoints. In earlier papers we have examined the details of the conversion of 4-substituted thianes[4] and 2-thiabicyclo-[2.2.1]heptane[5] to the diastereomeric S-oxides. We now record a related study on the oxidation of 2-methylthiolane (2-methyltetrahydrothiophene) (1).



1 2, cis 3, trans 4

Assignment of Configuration.—Pure samples of the isomeric sulfoxides **2** and **3** were obtained by careful elution chromatography on acid-washed alumina beginning, most conveniently, with mixtures in which one isomer was significantly more abundant. The structural assignments were based on three main lines of evidence: chromatographic retention times, nmr studies, and oxidation studies. The sulfoxides are highly hygroscopic liquids.

The isomer which exhibited the higher retention time on both column and vapor phase chromatography was assigned the trans structure **3**. Experience in our laboratories and others has shown that in the absence of complicating effects the isomer with the more sterically accessible sulfoxide oxygen has the higher retention time. Perhaps the most rigorous proof of structure comes from nmr studies summarized in Table I.

It is obvious from an inspection of the data of Table I that arguments based on the magnitude of chemical shifts would be ineffective for structural assignments. It has been assumed for some time that the anistropy of the S=O bond approximates that of the carbon–carbon triple bond. This assumption is probably a valid one, but the utility is limited by the less well understood screening by the free electron pair. The most effective data is provided by the benzene-induced shifts.[6,7] Ledaal[8] has recently proposed that benzene–polar solute collision complexes are best represented by a model with the positive end of the dipole of the polar functional group located along the sixfold axis of the benzene molecule. In the case of the sulfoxides in question, the deshielding of the methyl by the aromatic solvent should be more dramatic in the trans sulfoxide than in the cis (Figure 1). The interested reader is referred to an excellent group of recent articles dealing with penicillin sulfoxides.[9] The stereochemical assignment made here is entirely in line with arguments presented in detail in these papers concerning the steroechemistry of penicillin sulfoxides.

TABLE I

SOLVENT EFFECTS IN THE NMR SPECTRA OF 2-METHYLTHIOLANE AND DERIVATIVES[a]

Compd	Concn, mmol/ml	Solvent	δ_{CH_3}	J (Hz)	$(\delta' - \delta_{C_6H_6})$
1 (sulfide)	1.70	CCl_4	1.27	7.0	+0.11
		C_6H_6	1.16	7.0	
2 (cis sulfoxide)	1.70	DMSO-d_6	1.22	6.7	+0.04
		CCl_4	1.28	7.0	+0.10
		$CDCl_3$	1.40	6.5	+0.22
		C_6H_6	1.18	6.2	
3 (trans sulfoxide)	1.70	DMSO-d_6	1.13	7.3	+0.39
		CCl_4	1.19	7.0	+0.45
		$CDCl_3$	1.23	7.1	+0.49
		C_6H_6	0.74	7.2	
4 (sulfone)		CCl_4	1.27	7.0	+0.23
		C_6H_6	1.04	7.0	

[a] The spectra were run at ambient temperature using TMS as standard.

Infrared analysis of the 2-methylthiolane 1-oxides showed very minor differences outside the sulfoxide

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(4) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(5) C. R. Johnson, H. Diefenbach, J. E. Keiser, and J. C. Sharp, *Tetrahedron*, **25**, 5649 (1969).

(6) W. Amann and G. Kresge, *Tetrahedron Lett.*, 4909 (1968).

(7) E. J. Strom, B. S. Snowden, Jr., and P. A. Toldan, *Chem. Commun.*, 50 (1969); M. Nishio, *ibid.*, 51 (1969).

(8) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

(9) R. D. G. Copper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969); R. D. G. Cooper, P. V. DeMarco, and D. D. Spry, *ibid.*, **91**, 1528 (1969).