polarization, P_D, was calculated from the solution data[32] and the values were checked by calculation from the bond refractivities.[33]

Vapor Phase Chromatography.—The chromatograms were run with a Hi Fi chromatograph manufactured by Wilkins Instrument and Research, Inc., with a flame ionization detector. A 1.5-m. tube, 2 mm. in diameter, was packed with 60–80-mesh hexamethylene–disilazane-treated Chromasorb W with 2.5% Epon 1001. The column was maintained at 200° and the nitrogen flow-rate was 30 ml./min. Peaks appeared in the following order (minutes after injection): VII, 1.5; Thiodan-α, 5.0; XVI, 9.5; Thiodan-β, 13.5; and V, 23.0. The column factors for multiplication of the peak areas for the quantitative estimations are Thiodan-α, 1.00; Thiodan-β, 1.00; and V, 1.29.

Infrared Spectra.—The spectra were obtained with a Baird Model 4–55 apparatus, with samples incorporated in potassium bromide pellets, and in CS_2 on a Perkin-Elmer model 237 grating spectrophotometer.

X-Ray Diffraction.—The data was obtained with a Norelco Diffractometer equipped with a Geiger tube detector. Cu Kα radiation was used with a nickel filter at 35 kv. and 20 mamp. on a flat mounted sample in a nitrogen atmosphere. Slit adjustments were divergence, 1°; receiving, 0.003 in.; and scatter, 1°. There were no differences noted in the diffraction patterns obtained from V prepared from Thiodan-α or Thiodan-β.

N.m.r. Spectra.—These were obtained on a Varian A 60 apparatus equipped with a temperature probe with tetramethylsilane as the standard. The spectra were calibrated with the side bands from an audiooscillator.

Acknowledgment.—We are grateful to Professor Paul von Raugé Schleyer and Professor John D. Baldeschwieler for aid in the interpretation of the n.m.r. spectra, to Dr. Charles F. Ferraro for advice in the dipole moment studies, and to Dr. Robert C. Hopkins and Miss Yvonne DeWolf for help in programming.

(32) R. J. W. LeFevre, "Dipole Moments," Methuen and Co., Ltd., London, 1948, p. 19.

(33) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., London, 1957, p. 1036.

Organic Disulfides and Related Substances. XII. (2-Aminoethyldithio)benzoic Acids and Derivatives[1a,b]

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Syntheses and structural evidence are reported for the *ortho*, *meta*, and *para* isomers of (2-aminoethyldithio)-benzoic acid and for various derivatives. The *ortho* isomer was protective against lethal effects of ionizing radiation, but related substances were not. The *ortho* isomer exists in two isomorphic forms. Efforts to cyclize the *ortho* isomer to the eight-membered lactam gave polymeric products, susceptible to further polymerization, suggesting that the lactam readily breaks at the disulfide bond and subsequently polymerizes. Relative resistance of the various unsymmetrical disulfides toward disproportionation into symmetrical disulfides was examined, and correlations are suggested between the degree of resistance and structural features. Preparation of aromatic thiolsulfonates using the chlorinolysis procedure developed by Douglass and Farah for aliphatic disulfides usually was quite effective.

In a continuing study of disulfides and thiolsulfonates,[1b] *o*-(2-aminoethyldithio)benzoic acid (**1**) and related compounds became of interest for several reasons (most of these compounds are shown in Charts I and II). (1) Unsymmetrical disulfides undergo disproportionation according to the following general equation.[2] Information about the disproportionation

$$2RSSR' \rightleftharpoons RSSR + R'SSR'$$

of disulfides here reported should lead to better understanding of factors which play a role in the stability of unsymmetrical disulfides. (2) The acid **1** and its congeners offered promise of worthwhile protection against lethal effects of ionizing radiation, owing to presence in an unusual environment of the 2-aminoethylthio moiety, which frequently confers protective activity.[3] (3) Several considerations led to interest in conversion of the acid **1** to its lactam **2**. First, 1,2-dithiacyclooctane polymerizes readily in what amounts to a disproportionation,[4,5] and it was worthwhile to learn whether incorporation of an aromatic disulfide and an electron-withdrawing amide moiety would stabilize or destabilize such a system. Secondly, the less polar lactam (**2**) should traverse membrane barriers better than the zwitterionic acid **1** and thus might be more protective against radiation. Finally, models show that the lactam **2** should be dissymmetric; resolution of **2** or a suitable derivative thus would provide the first chemical evidence of optical activity dependent on a sulfur–sulfur bond.

The acid **1** was synthesized by thioalkylation of *o*-mercaptobenzoic acid by a 2-aminoethyl thiolsulfonate (**3**), as shown in Chart I. The acid **1** proved to be "good" in protective capability,[6a] thus lending early encouragement to an extensive study of related disulfides.

Initial work in the synthesis of the acid **1** was quite puzzling, because two products resulted (**1A** and **1B**). They differed in melting point and infrared spectra. Compound **1A**, obtained first, changed during recrystallization to **1B**, which had an infrared spectrum like that of **1A** except for three new bands and for loss

(1) (a) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1962. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (b) Paper XI: L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964). (c) Texaco Fellow in Chemistry, 1961-1962; abstracted from a portion of the Ph.D. Dissertation of R. R. C., Vanderbilt University, 1963. (d) To whom correspondence should be addressed.

(2) For discussion see L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

(3) *Cf.* J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962.

(4) J. G. Affleck and G. Dougherty, *J. Org. Chem.*, **15**, 865 (1950).

(5) A. Schöberl and H. Gräfje, *Ann.*, **614**, 66 (1958).

(6) (a) Protective activities against ionizing radiation were provided through the kindness of Drs. T. R. Sweeney and D. P. Jacobus of the Walter Reed Army Institute of Research, Washington, D. C. General procedures and the meaning of activity ratings have been described earlier.[6b] (b) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

CHART I

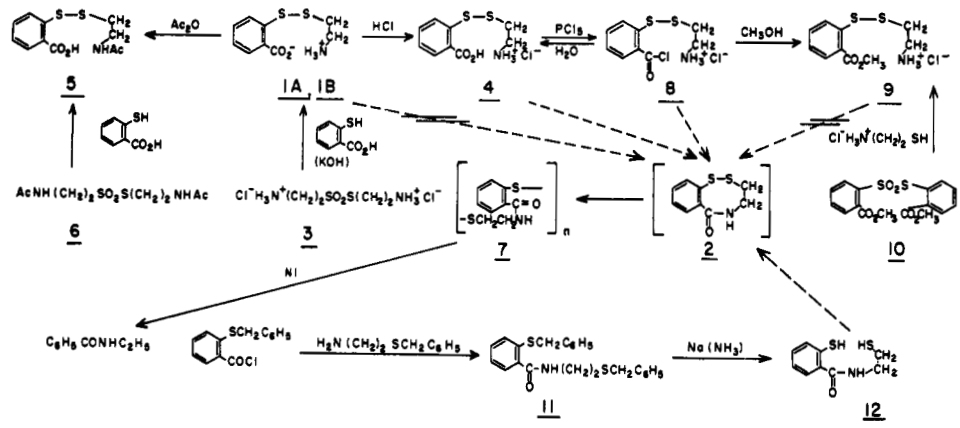
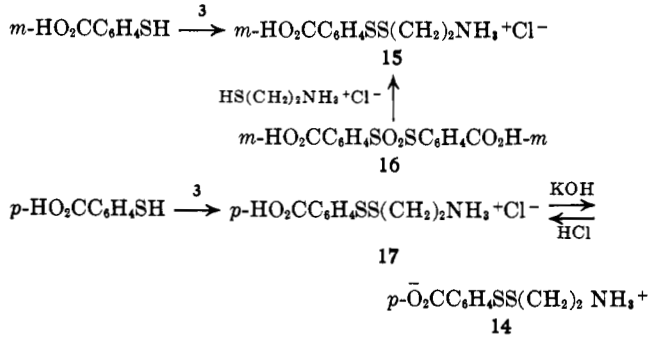


CHART II



of one band. Compound **1B** gave a hydrochloride which upon neutralization returned **1A**. Another puzzling feature was that both **1A** and **1B** unexpectedly consumed iodine; the end point was indistinct, but about 1.6 g.-atoms of iodine was consumed per mole of **1A** or **1B**.

An early thought was that **1A** might have disproportionated to the two symmetrical disulfides, cystamine and 2,2′-dithiodibenzoic acid, and that **1B** might be a salt of these. A 1:1 molar mixture (**1C**) therefore was prepared from cystamine dihydrochloride and 2,2′-dithiodibenzoic acid disodium salt. Salt **1C** differed from **1A** and **1B** in several respects. (1) The melting point was much lower and was without decomposition. (2) The infrared spectrum, although similar, showed significant differences. Ultraviolet absorption was seen at 210, 245, and 295 mμ (log ϵ_{295} 3.37); both **1A** and **1B** absorb in this region only at 290 mμ. (3) It is about ten times as soluble in water. (4) Behavior of salt **1C** with hydrochloric acid or upon acetylation differs markedly (*cf.* Experimental).

Evidently **1A** and **1B** are isomorphic forms of the acid **1**. The following evidence is given for their isomorphism, which also supports the various interrelated structures. (1) The same synthesis gave **1A** twice and **1B** once, both having appropriate analyses and neutralization equivalents. Only slight differences in procedure determine whether **1A** or **1B** results. (2) Solution properties of isomorphs must be identical. Ultraviolet spectra of aqueous solutions of **1A** and **1B** were identical and met expectation (the sodium salt of 2,2′-dithiodibenzoic acid absorbs at 296 mμ[7]; both **1A** and **1B** have log ϵ_{290} 3.31). Ultraviolet spectra were not definitive, however, because structures like **1** would have similar chromophores. Infrared and Raman spectra of **1A** and **1B** in solution were inconclusive owing to sparing solubilities. (3) An early product containing both **1A** and **1B** showed far-infrared bands at 538 (w), 490 (m, sh), and 470 (s, b) cm.$^{-1}$, in the region of 550 to 400 cm.$^{-1}$ associated with disulfide linkages; no absorption was seen in the region of 2550 cm.$^{-1}$ associated with thiol absorption.[8,9] More definitive evidence for absence of a thiol group was provided by a negative nitroprusside test with both **1A** and **1B**. All of this evidence substantiated structure **1** and eliminated concern that a thiol group was present, which had been suggested by iodine consumption. (4) Dissolution of **1A** or **1B** in dilute acid or base followed by neutralization returned **1A** or **1B** unpredictably, occasionally mixtures of both. (5) As shown by Chart I, both **1A** and **1B** gave the same hydrochloride salt (**4**). The hydrochloride (**4**) was synthesized independently from *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate and 2-mercaptoethylamine hydrochloride. (6) As shown by Chart I, acetylation of either **1A** or **1B** gave the same N-acetyl derivative (**5**), the structure of which was confirmed by independent synthesis from 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**6**) and *o*-mercaptobenzoic acid.

The structure of the acid **1** having been established, conversion to the lactam **2** was attempted. 1,3-Dicyclohexylcarbodiimide or water-soluble 1-cyclohexyl-3-[2-(4-morphinyl)ethyl]carbodiimide metho-*p*-toluenesulfonate gave either two symmetrical disulfides or intractable mixtures. Equally unpromising cyclizations were attempted by heating in organic solvents or by using N-ethyl-5-phenylisoxazolium-3′-sulfonate.[10]

The hydrochloride (**4**) with a carbodiimide and triethylamine gave insoluble presumably polymeric product (*e.g.*, structure **7** of Chart I). Formation of the amide linkage was proved by desulfurization of the polymer with Raney nickel to N-ethylbenzamide, suggesting that lactam **2** was present momentarily although the polymer also could have resulted from *inter*molecular condensation of carboxyl and amine groups.

(7) L. Schotte, *Arkiv Kemi*, **9**, 299 (1956).

(8) We are indebted to Dr. M. B. Berenbaum and Mr. E. Barsum of the Trenton laboratories of the Thiokol Chemical Corp. for these spectra.

(9) Absorptions are given in cm.$^{-1}$. Abbreviations signify: s, strong; m, medium; w, weak; b, broad; sh, shoulder.

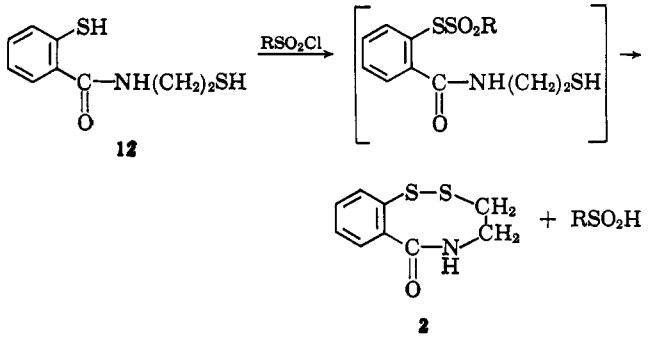
(10) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).

Cyclization also was attempted *via* the acid chloride (**8**), the structure of which was confirmed by hydrolysis to **4** and by methanolysis to **9**, itself synthesized independently from the thiolsulfonate **10** and 2-mercaptoethylamine hydrochloride. Bases tried for cyclization of **8** included pyridine, triethylamine, sodium hydroxide, and potassium acetate. Some products were partly soluble in organic solvents, but the lowest molecular weights obtained were about twice that of the lactam **2**. Solutions of the products deposited solid on heating and even on standing, suggesting further polymerization. Thin layer chromatography gave no indication of lactam **2**. In general, all products resembled those mentioned above (and formulated as **7**) in infrared spectrum, melting point, and insolubility, although some products seemed to be dimers or low polymers subject to further polymerization. Early attempts to cyclize the free base of the ester **9** were unpromising.

An alternative formation of lactam **2** by oxidation of a dithiol containing the amide linkage also was explored. The dibenzyl derivative **11**, prepared in good yield from the known S-benzyl derivatives shown in Chart I, gave the requisite dithiol **12**.

Schöberl and Gräfje reported synthesis of 1,2-dithiacyclooctane by slow addition of the corresponding dithiol to ferric chloride and acetic acid.[5] In a procedure closely simulating theirs, the dithiol **12** gave polymer; a fraction polymerized further under mild conditions. Oxidation with iodine at high dilution afforded no better results.

Part of the difficulty in obtaining lactam **2** by oxidation may lie in the fact that the dithiol **12** contains different types of thiol groups which undoubtedly differ in oxidation potential. In an effort to circumvent this difficulty, conversion of the dithiol with *p*-toluenesulfonyl chloride to a monothiolsulfonate was considered. Hopefully, the monothiolsulfonate would be attacked immediately intramolecularly by the thiol group, as shown by the following equation. Several



variations of this approach failed, although it was the most promising tried in that it yielded more soluble and more sharply melting products.

To summarize, the possibility seems remote that lactam **2** can exist as a stable monomer, although it probably was in hand momentarily. As mentioned, two groups of investigators have placed 1,2-dithiacyclooctane in a reactive class, *vis-à-vis* its tendency to polymerize.[4,5] Assuming that the lactam **2** was produced in the syntheses, therefore, one may conclude that incorporation of an aromatic amide into such a system has no significant effect in increasing stability and indeed probably decreases it.

The good radio-protective action afforded by disulfide **1** prompted synthesis also of its *meta* and *para* analogs, **13** and **14**. These syntheses proved much less straightforward than anticipated. In contrast to the *ortho* acid **1**, the *meta* isomer **13** proved to be quite soluble in water and could not be isolated by the procedure used for the *ortho* isomer **1**. However, the hydrochloride salt (**15**) could be obtained using thiolsulfonate **3**, as shown in Chart II, after tedious removal of taurine ($H_2NCH_2CH_2SO_3H$), hypotaurine ($H_2NCH_2CH_2SO_2H$), unchanged **3**, and other water-soluble by-products. The alternative route of Chart II, from the aromatic thiolsulfonate **16** and 2-mercaptoethylamine hydrochloride, gave purer disulfide **15** in better yield, however, and is by far the method of choice. This experience, and a similar good result in the synthesis of the *ortho* analog **4**, suggest the important generalization that unsymmetrical aryl disulfides such as **4** and **15** may be prepared best by reaction of an aryl thiolsulfonate with the aminothiol hydrochloride, rather than by the alternative route from a thiophenol; the purification should be far simpler because the arenesulfinic acid by-product can be extracted easily into ether, unlike the aminoalkanesulfinic acid by-product.

A digression is worthwhile here. This paper reports syntheses of *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate and its *meta* isomer (**16**), as well as of the ester (**10**) of the *ortho* acid, by the useful procedure for chlorinolysis of aliphatic disulfides developed by Douglass and Farah.[11a] We have obtained analogous arenethiolsulfonates in good yields by this method which contain the groups *p*-CH_3,[2] *p*-Cl,[11b] *p*-NO_2,[11b] and H.[11b] These results in the preparation of seven aromatic thiolsulfonates point to the general utility of the Douglass–Farah method in the aromatic series, as well as in the aliphatic series; however, the method gave poor results with 4,4′-dithiodibenzoic acid. Successful preparation of the two carboxyarenethiolsulfonates mentioned is especially noteworthy, since the Douglass–Farah method requires participation of a stoichiometric quantity of acetic acid so that carboxyl groups in the disulfide might have been thought to interfere.

Synthesis of the *para* acid **14** was achieved, *via* its hydrochloride (**17**), as shown in Chart II. *p*-Mercaptobenzoic acid was used in grossly impure form because it was difficult to form and to separate from 4,4′-dithiodibenzoic acid, the corresponding disulfide. Fortunately, the properties of the various substances were such that the 4,4′-dithiodibenzoic acid could be separated quite easily from the amino acid **14**.

Solubility behavior shows that the unsymmetrical disulfides prepared are homogeneous compounds and not eutectic mixtures or molecular compounds of symmetrical disulfides. For example, had the unsymmetrical disulfides (**1**, **14**, and **15** base) containing nonacetylated amino groups been mixtures, dissolution of the hydrochloride salts in water or of the zwitterions in acid, which occurred easily, would have been incomplete. Similarly, had the acylated amino disulfide **5** been a mixture, the symmetrical aliphatic disulfide should have been readily extractable into water; in contrast, **5** is but sparingly soluble.

(11) (a) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959). (b) Ph.D. Dissertation of T. F. Parsons, Vanderbilt University, May 1964.

Further evidence for homogeneity of the disulfides prepared is provided by infrared spectra. The spectra of the unsymmetrical disulfides are similar to those of the symmetrical disulfides. Differences are readily apparent, however; new absorptions occur and also, in some instances, absorptions of the symmetrical compounds are absent.[12]

For studies of disproportionation, solutions of disulfides were heated at 100°. The extent of disproportionation was determined by recovery of a symmetrical disulfide. Results are summarized in Table I in approximate decreasing stability for classes and within each class. Values are not recorded for sodium salts of the acids because they decomposed (much hydrogen sulfide evolved upon acidification after heating).

Dissolution of the unsymmetrical disulfide hydrochlorides in water often left a little colloidal symmetrical aryl disulfide, but the amount was inconsequential. For example, the least stable disulfide studied, **4**, was less than 5% disproportionated after 3 hr. in solution at about 25°. Disproportionation of solutions of the disulfides in Table I thus is unlikely to be troublesome under ambient conditions.

TABLE I
DISPROPORTIONATION OF DISULFIDES, RSSR'[a]

No.	Comp.	—Disproportionation, %[b]— 3 hr.	22 hr.
	Amides		
5[c]	*o*-AcNH(CH$_2$)$_2$SSC$_6$H$_4$CO$_2$H	6	13
18[c]	*p*-AcNH(CH$_2$)$_2$SSC$_6$H$_4$CH$_3$	7	25
	Zwitterionic structures		
14	*p*-H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2^-$	1	4
1A[d]	*o*-H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2^-$	12	21
1B[d]	*o*-H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2^-$	17	24
13[e]	*m*-H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2^-$	40	45
	Hydrochloride salts		
9	*o*-Cl$^-$H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2$CH$_3$	9	51
15	*m*-Cl$^-$H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2$H	31	79
17[f]	*p*-Cl$^-$H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2$H	46	96
4	*o*-Cl$^-$H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CO$_2$H	51	95
19[g]	*p*-Cl$^-$H$_3$N$^+$(CH$_2$)$_2$SSC$_6$H$_4$CH$_3$	68[h]	

[a] In approximate order of decreasing stability for classes and within each class. [b] Calculated as (100 × 2 × moles of either symmetrical disulfide isolated)/(moles of unsymmetrical disulfide used). [c] Ethanol solution. [d] Values for **1A** and **1B** should be equal in solution; differences presumably reflect experimental error. [e] Prepared by treating the hydrochloride **15** with 1 equiv. of 0.1 *N* sodium hydroxide and used *in situ*. [f] Prepared by treating **14** with 1 equiv. of 0.1 *N* hydrochloric acid and used *in situ*. [g] *Cf.* ref. 2 for preparation. [h] After 2.75 hr. at 104°.[2]

The studies of disproportionation are not definitive, but several observations are worth mentioning. (1) Acetylation of the amine greatly stabilizes an aminodisulfide relative to its hydrochloride (compare **5** with **4** and **18** with **19**). This greater stability of amides than of hydrochlorides confirms an earlier inference,[1b] but the earlier caution is appropriate regarding the possible effect of the difference in solvents needed for the amides (ethanol) and hydrochlorides (water)[1b]; *gem*-bisdisulfides are less stable in water than in alcohol, but limited experience with other disulfides suggests that the two solvents usually will give similar results when both can be used.[1b,11b] (2) Electron-withdrawing groups in the aryl moiety seem to have a stabilizing influence toward thermal disproportionation in ambient light (although the nitro group has a destabilizing influence in the dark[11b]); compare the *p*-tolyl compound **19** with the *p*-carboxy analog **17**. (3) Comparison of **4**, the *ortho* acid hydrochloride, and its ester **9** suggests that esters confer greater resistance than do carboxylic acids. (4) For the amphoteric amino acids, **1**, **13**, and **14**, the zwitterionic forms seem more stable than their hydrochloride salts. The explanation may be that the disproportionated products of the zwitterions are water-soluble amine salts (no solids precipitated in any of these instances), so that formation of sparingly soluble products does not force the equilibrium to the right as occurs with the hydrochloride salts (solids precipitated in all of these instances); the disproportionation of the zwitterions thus may be reversible rather than essentially irreversible. (5) The unsymmetrical disulfides mentioned all seem to have good stability as solids, and no significant disproportionation occurred when the solids were stored for extended periods; this observation accords with that for other disulfides.[2]

We emphasize here, as elsewhere,[1b] that correlations of the foregoing kind are intended as practical guideposts for working with unsymmetrical disulfides in solvents and under conditions likely to be used in actual practice. For eventual theoretical interpretation, once general features are clearer, it will be desirable to use a single solvent for comparisons, to control incident light, to distinguish between reversible and essentially irreversible disproportionation, etc.

The structural specificity required for the good protective activity of the *ortho*-zwitterionic structure **1** against radiation is remarkable. All related compounds reported here were inactive for protection (**5**, **9**, **10**, **12**, **14**, **15**, **18**, and **19**).[6a] Since a decylaminoethyl thiolsulfonate, like the aminoethyl thiolsulfonate **3**, had proved "good" in protective activity,[6b] *o*-(2-*n*-decylaminoethyldithio)benzoic acid (**20**) was synthesized; even it was inactive. Study is in progress of *ortho*-substituted systems in which the carboxyl group of **1** is replaced by other groups; slight to fair activity already has been obtained.

Experimental[13]

Preparation of Thiolsulfonates Using Chlorine. A. *o*-Methoxycarbonylphenyl *o*-Methoxycarbonylbenzenethiolsulfonate (10).—In a procedure like that of Douglass and Farah,[11a] chlorine (55.8 g., 35.9 ml.) was introduced slowly (90 min.) as a gas into a stirred mixture at 0−5° of dimethyl 2,2′-dithiodibenzoate[14] (131.5 g.) and acetic acid (23.7 g.) in methylene chloride (200 ml.). The mixture was stirred for an additional 10 min. at 0°, after which water (14.2 ml.) was added slowly with vigorous stirring. The suspension was kept at *ca.* 20 mm. for 12 hr. and

(12) For example, the following absorptions of the symmetrical aromatic disulfides are absent in those of the unsymmetrical disulfides[9]: **4**, 697 m, 740 s, 1263 s, 1272 s; **15**, 1450 s (appears as slight shoulder in the unsymmetrical disulfide); **17**, 710 w, 1125 m, 1135 m, 1190 s; **9**, 976 m, 1111 s; **5**, 742 s, 910 m, b.

(13) Melting points are corrected. Decomposition points were determined by immersion of the sample about 10° below the decomposition point and then heating so that the temperature rose *ca.* 2-3°/min. Elemental analyses and molecular weights (determined in chloroform with a Mechrolab osmometer) were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137B Infracord spectrophotometer with films of liquids or Nujol mulls of solids. Ultraviolet spectra were done using a Cary Model 14 spectrophotometer.

(14) Eastman technical grade recrystallized (Darco) from ethyl acetate; the reaction failed with unpurified material.

then was triturated under cold water–methanol (2:1, 250 ml.). Collection by filtration and recrystallization from ethanol gave 120.5 g. (84%) of **10** as tan needles, m.p. 98.5–100°, identical with an analytical sample obtained similarly but with omission of methylene chloride (which resulted in material of m.p. 88–128°). Pure **10** had a constant melting point of 101–102° and showed strong infrared bands at 1152, 1335, 1725, and 1758 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{14}O_6S_2$: C, 52.44; H, 3.85; S, 17.50. Found: C, 52.65; H, 3.86; S, 17.60.

B. *m*-Carboxyphenyl *m*-Carboxybenzenethiolsulfonate (16).—3,3′-Dithiodibenzoic acid was prepared from *m*-aminobenzoic acid by a procedure reported for the *para* analog.[15] The crude *meta* compound precipitated as gum, but extraction with ethanol gave the *meta* disulfide in 80% yield, m.p. 213–220° (lit.[16] m.p. 246°). The crude 3,3′-dithiodibenzoic acid (53.9 g.) was oxidized to the thiolsulfonate **16** by the procedure used for **10**. After evaporation of the methylene chloride, the solid residue was triturated under five 250-ml. portions of cold water, separated by filtration, and dried, yielding **16**, 54.8 g. (92%), m.p. 210–211° dec. Recrystallization gave **16** having m.p. 220° dec. (lit.[16] m.p. 220°). The infrared spectrum had strong bands at 1345, 1164, and 1138 cm.$^{-1}$. Attempts to prepare the *para* analog of the thiolsulfonate **16** by the same procedure resulted mainly in unchanged disulfide.

C. *o*-Carboxyphenyl *o*-Carboxybenzenethiolsulfonate.—By the procedure used for **10**, 2,2′-dithiodibenzoic acid (30.0 g.)[17] was oxidized to the thiolsulfonate. Evaporation of the methylene chloride gave crude *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate (21.8 g., 66%), m.p. 216–221° dec. (lit.[18] m.p. 228° for the "disulfoxide"). Recrystallization (aqueous ethanol, 25°) resulted in m.p. 218–222° dec.; strong infrared absorption at 1152, 1164, and 1338 cm.$^{-1}$.

Each of the thiolsulfonates produced in A, B, and C gave an acidic reaction when treated with a thiol, a reaction considered a useful test for thiolsulfonates.[19]

***o*-(2-Aminoethyldithio)benzoic Acid (1). A. Preparation of (1A).**—A solution of 65.2 g. of *o*-mercaptobenzoic acid in 650 ml. of ethanol was added rapidly with stirring to 109 g. of 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (**3**)[2] in 400 ml. of 1:1 ethanol–water, and the mixture was then stirred for 3.5 hr. Evaporation below 30° gave gummy solid, which was rubbed with ether several times; it was then dissolved in water, and ether was added. After addition of a cold solution of 47.4 g. of potassium hydroxide in 540 ml. of water, several minutes of shaking resulted in a transient green-black color and then in the precipitation of 63.5 g. of **1A** (conversion, 66%; yield 77%, based on recovered symmetrical aryl disulfide in the ether): m.p. 204–205° dec.; strong, infrared absorption at 738 cm.$^{-1}$, but none at 3550, 758, or 750 cm.$^{-1}$.

Six recrystallizations of this **1A** from water (about 34 ml./g. at 100°) and from water–ethanol gave solid of progressively lower melting point. The final product had m.p. 198–200° dec.; this substance was termed **1B**. The infrared spectrum of **1B** contained the following bands, among others[9]: 1640 s, 1608 sh, 1043 s, 758 s, 750 s, 3550 m, 1290 m, 905 m, 844 m, 820 m, 707 m, and 694 m.

Anal. Calcd. for $C_9H_{11}NO_2S_2$: C, 47.15; H, 4.84; N, 6.11; S, 27.98. Found: C, 46.95; H, 5.04; N, 5.86; S, 27.87.

When 5.0 g. of the thiosulfonate **3** and 3.0 g. of *o*-mercaptobenzoic acid were treated exactly as described above, the crude product (78% yield) again proved to be **1A** (infrared spectrum and m.p. 205° dec.).

B. Purification of 1A for Analysis.—The hydrochloride of **1** (2.7 g.; *cf.* below for preparation from **1B**) in water (15 ml.) was neutralized with 1 equiv. of 0.1 *N* sodium hydroxide during scratching and seeding with crude **1A**. Chilling and filtration yielded needles of **1A** (1.8 g., 78%), m.p. 205° dec. The infrared spectrum was identical with that of crude **1A** and contained the following bands, among others[9]: 1600 s, 820 s, 738 s, 1647 m, 1282 m, 1042 m, 900 m, 839 m, 704 m, and 691 m.

Anal. Calcd. for $C_9H_{11}NO_2S_2$: C, 47.15; H, 4.84; neut. equiv., 229. Found: C, 47.21; H, 4.78; neut. equiv. (formol), 230.

C. Preparation of 1B.—*o*-Mercaptobenzoic acid (98 g.) in nearly boiling ethanol (600 ml.) was added over 10 min. to 163.9 g. of thiolsulfonate **3** in water–ethanol (350:50). The reaction temperature was kept below 29° by cooling. The mixture was stirred for 4 hr. and then was neutralized below 29° with a cold solution of potassium hydroxide (71.3 g.) in water (500 ml.). After 20 min. of stirring at 0°, ether (100 ml.) was added to initiate precipitation, which began in about 15 min. The mixture was stirred at 0° for 2 hr. The solid was separated and washed with water and ethanol, yielding 108.5 g. (74%) of finely crystalline **1B**: m.p. 197–199° dec.; strong infrared bands at 3550, 758, and 750, but none at 738 cm.$^{-1}$. This **1B** was identical (infrared spectrum and mixture melting point) with the analytical sample described above. Two recrystallizations gave **1B** with m.p. 198° dec.; neut. equiv. (formol), 235 (calcd., 229).

D. Cystamine 2,2′-Dithiodibenzoate (Salt 1C).—Cystamine dihydrochloride (3.62 g.) in water (10 ml.) was added to 2,2′-dithiodibenzoic acid (4.92 g.)[17] in 0.37 *N* sodium hydroxide solution (87 ml.). The salt formed upon chilling (6.65 g., 90%) had m.p. 165° and an infrared spectrum very similar to that of **1B**. Trituration of salt **1C** (0.43 mmole) under 0.1 *N* hydrochloric acid (0.86 mmole) left the symmetrical aryl disulfide (0.43 mmole, 100%); in contrast, dissolution of **1A** or **1B** in acid is complete. Acetylation of salt **1C**, as described below for **1A** or **1B**, gave acetyl cystamine and the symmetrical aryl disulfide in 47 and 99% yields, respectively.

***o*-(2-Aminoethyldithio)benzoic Acid Hydrochloride (4). A. From 1A and 1B.**—A suspension of **1A** (8 g.) in water (40 ml.) was treated with 1 equiv. of 0.4 *N* hydrochloric acid, and a little colloidal material was removed using Darco. Lyophilization and recrystallization from absolute ethanol gave **4** in nearly quantitative yield as needles: constant m.p. 200–201°; typical infrared absorption at 688, 752, 1150, 1240, and 1698 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}ClNO_2S_2$: C, 40.67; H, 4.55. Found: C, 40.86; H, 4.84.

Treatment of **1B** (35 g.) in the manner used for **1A** gave **4** (38.8 g., 96%), identical with the analytical sample from **1A** above (mixture melting point and infrared spectrum).

The same hydrochloride **4** also was obtained by treating either **1A** or **1B** (or mixtures) with 20% hydrochloric acid; initial solution was followed by rapid precipitation.

B. From *o*-Carboxyphenyl *o*-Carboxybenzenethiolsulfonate.—A solution of *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate (0.97 g.) in ethanol (4 ml.) was added with stirring to a solution of 2-mercaptoethylamine hydrochloride (0.315 g.) in ethanol (2 ml.). After 4 min., ether (35 ml.) was added. Chilling gave a solid (0.59 g., 80%), m.p. 195–199°, identical (mixture melting point and infrared spectrum) with the hydrochloride **4** described above. Neutralization of the hydrochloride **4** from this route with 1 equiv. of dilute base gave **1A** (infrared spectrum and m.p. 205° dec.).

Attempts to Cyclize 1 and 4.—Of ten attempts at cyclization, the following is typical. Triethylamine (5 mmoles) was added to a stirred solution of **4** (5 mmoles) and 1,3-dicyclohexylcarbodiimide (5 mmoles) in methanol (100 ml.). After a stirring period of 115 hr., filtration yielded a white solid (25%), m.p. 241–242° (Kofler), insoluble in all of numerous solvents tried and having an infrared spectrum identical with that of polymer **7** (*vide infra*). The only other product identified was N,N′-dicyclohexylurea. A mixture of the insoluble product (0.18 g.) and Raney nickel (4 g.) in ethanol (50 ml.) heated at reflux for 25 hr. yielded an oil which, when triturated under acetone, gave solid (0.12 g., 94%), m.p. 67–70°, identical (infrared spectrum and mixture melting point) with authentic N-ethylbenzamide.

***o*-(2-Acetamidoethyldithio)benzoic Acid (5). A. From 1A and 1B.**—A suspension of **1A** (2.5 g.) in pyridine (8.8 ml.) containing acetic anhydride (15.7 g.) was stirred overnight. Dilution with water and evaporation (below 40°) gave 2.2 g. (75%) of solid, m.p. 147–149°. Recrystallization from acetone–water gave **5** as needles, m.p. 149.5–150.5°, identical (mixture melting point and infrared spectrum) with authentic **5** prepared as described in B.

The zwitterion **1B** (2.5 g.) treated essentially as above gave crude **5** in 80% yield, m.p. 144–145°; recrystallization gave needles, m.p. 150–151°, identical (mixture melting point and infrared spectrum) with **5** prepared as described in B.

(15) E. Campaigne and W. W. Meyer, *J. Org. Chem.*, **27**, 2835 (1962).

(16) S. Smiles and J. Stewart, *J. Chem. Soc.*, **119**, 1792 (1921).

(17) Eastman practical grade purified by reprecipitation from 1.3 *N* base and recrystallization from 1-butanol.

(18) T. P. Hilditch, *J. Chem. Soc.*, **97**, 2579 (1910).

(19) *Cf.* L. Field, T. F. Parsons, and R. R. Crenshaw, *J. Org. Chem.*, **29**, 918 (1964).

B. From Thiolsulfonate (6).—A warm (43°) solution of *o*-mercaptobenzoic acid (8.64 g.) in ethanol (85 ml.) was added rapidly with stirring to 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**6**, 15 g.)[2] in 1:1 ethanol–water (50 ml.). After 4 hr., the solution was evaporated below 40° to an oil. The oil was suspended in chloroform and washed with aqueous bicarbonate (4.7 g. in 150 ml. of water) and water. Drying and evaporation left sticky solid, which was triturated with cold water and dried, yielding **5**, 11.03 g. (73%), m.p. 128–130°. One recrystallization from 1:1 ethanol–water yielded 10.55 g. of crystalline solid: m.p. 130–133° after being dried at 25°; m.p. 148–149° after being dried at 56° (0.1 mm.) for 12 hr. Several recrystallizations gave **5** with constant m.p. 150.5–151.5°.

Anal. Calcd. for $C_{11}H_{13}NO_3S_2$: C, 48.68; H, 4.83; neut. equiv., 271. Found: C, 48.87; H, 4.72; neut. equiv., 277.

***o*-(2-Aminoethyldithio)benzoyl Chloride Hydrochloride (8).**

A. Preparation.—A suspension of 5.0 g. of **4** and 5.3 g. of phosphorus pentachloride in acetyl chloride (52 ml.) was stirred for 4 hr. and then was diluted with carbon tetrachloride. The solid was separated and washed well by rubbing with carbon tetrachloride, yielding **8** as a white solid, 4.1 g. (77%), m.p. 130° dec. Structure **8** for the product is supported by two strong peaks in the infrared spectrum at 1765 and 1730 cm.$^{-1}$.

Any symmetrical 2,2′-dithiodibenzoyl chloride, a possible alternative structure which might have formed *via* disproportionation, should have been removed by the carbon tetrachloride; moreover, **8** dissolved completely in water (evaporation gave the original carboxylic acid hydrochloride **4**), whereas 2,2′-dithiodibenzoyl chloride should not dissolve in water.

B. Methyl *o*-(2-Aminoethyldithio)benzoate Hydrochloride (9).—Identity of the aroyl chloride **8** was confirmed by allowing 1.3 g. of **8** in 48 ml. of methanol to stand for 22 hr. Evaporation gave the ester **9** (66%, m.p. 110°), which after recrystallizations from 1-butanol–cyclohexane had m.p. 121–124°.

For independent synthesis of the ester **9** a solution of 2-mercaptoethylamine hydrochloride (15.5 g.) in water (55 ml.) was added, with stirring over 40 min., to 50.0 g. of the thiolsulfonate **10** in ethanol (450 ml.). The mixture was stirred for 70 min. more and then was concentrated below 38° to leave a sirup, which was taken up in chloroform and cold aqueous base (0.273 mole of potassium hydroxide in 350 ml. of water). The chloroform layer was immediately extracted with 0.41 *N* hydrochloric acid (334 ml.). Evaporation of the acid extract below 38° left a glass which, when triturated under acetone, yielded 16.8 g. (44%) of white solid **9**, m.p. 124–126°. Several recrystallizations from 1-butanol–cyclohexane gave **9**, constant m.p. 124.5–126.5°. Mixture melting point and identical infrared spectrum showed this **9** to be identical with that from the aroyl chloride **8**.

Anal. Calcd. for $C_{10}H_{14}ClNO_2S_2$: C, 42.93; H, 5.04. Found: C, 42.80; H, 5.14.

Other reaction products were mainly the two symmetrical disulfides; if extractions are not carried out rapidly, the yield of **9** is greatly lowered, presumably because of their formation. Chloroform, rather than ether, facilitated rapid extraction and its use nearly doubled the yield of **9**.

C. Attempts to Cyclize 8.—Of eight attempts at cyclization of **8** to the lactam **2**, the following is typical. Addition over 3 hr. of 2.28 g. of solid **8** to 366 ml. of a stirred aqueous solution of sodium hydroxide (16.1 mmoles) yielded 1.0 g. of polymeric precipitate (**7**), m.p. 105–140°; the infrared spectrum was consistent with an amide grouping. The aqueous layer contained only hydrolysis products of **8**. Chloroform at 25° extracted from the 1.0 g. of solid a semisolid, which failed to redissolve completely when the chloroform was removed; numerous fractional extractions and precipitations of material which did redissolve in chloroform yielded, as the only promising product, 50 mg. of yellow solid, m.p. 48–55°.

Anal. Calcd. for $C_9H_9NOS_2$ (**2**): mol. wt., 211. Found: mol. wt., 467.

Sealed solutions became turbid in 3 days and deposited solid in 1 month, indicating further polymerization.

When crude product **7** from a similar experiment was dissolved in boiling dimethylformamide, a precipitate separated in a few minutes which had m.p. 243–246° dec. and was insoluble in other solvents.

Anal. Calcd. for $(C_9H_9NOS_2)_n$: C, 51.16; H, 4.29; S, 30.35. Found: C, 51.21; H, 4.91; S, 30.35.

***o*-Benzylthio-N-(2-benzylthioethyl)benzamide (11).**—To a partial solution at 15° of 76.7 g. of *o*-(benzylthio)benzoyl chloride[20] and 29.5 g. of triethylamine in 1 l. of dry benzene, there was added with stirring 54.7 g. of 2-(benzylthio)ethylamine,[22] b.p. 91–92° (0.5 mm.). The mixture was heated at reflux for 1 hr. After removal of precipitate, evaporation left a solid which was recrystallized from 82% ethanol (1100 ml.) to yield **11**: 96.6 g. (84%); m.p. 103.5–104.5°; constant melting point after further recrystallization, 104.5–105.5°.

Anal. Calcd. for $C_{23}H_{23}NOS_2$: C, 70.19; H, 5.89. Found: C, 70.35; H, 5.93.

***o*-Mercapto-N-(2-mercaptoethyl)benzamide (12). A. Preparation.**—Small freshly cut portions of sodium were added to 40.0 g. of the amide **11** in 520 ml. of liquid ammonia until a permanent blue color persisted at least 30 min.; 7.2 g. of sodium was required. A small amount of ammonium chloride was added to destroy excess sodium. A water solution (300 ml.) of the residue was washed with ether and then acidified with 10% hydrochloric acid. An ether extract of **12** gave 20.55 g. (94%) of **12** as an oil, iodine titer 93% of theory, $n^{25}D$ 1.6185.

Short-path distillation (105°, 0.03 mm.) gave **12** as a deep yellow oil, $n^{25}D$ 1.6314, iodine titer 98.5% of theory; the product isolated after titration was quite similar in infrared spectrum to polymeric amide **7**, thus substantiating the structure of **7**.

Anal. Calcd. for $C_9H_{11}NOS_2$: C, 50.67; H, 5.20; N, 6.57; mol. wt., 213. Found: C, 50.52; H, 4.98; N, 6.74; mol. wt., 203.

All subsequent handling was under nitrogen; the material could be stored unchanged at least for several weeks under nitrogen.

B. Attempts to Cyclize 12.—Ferric chloride was used essentially as by Schöberl and Gräfje for the synthesis of 1,2-dithiacyclooctane.[5,23] The dithiol **12** (1 g.) in ether (100 ml.) was added over 5 days to a stirred solution at reflux of ferric chloride hexahydrate (3.8 g.) and acetic acid (5 ml.) in ether (200 ml.). After 12 hr. more at reflux, filtration yielded solid which was washed with water, 0.8 g., m.p. 138–147°; the infrared spectrum was indistinguishable from that of polymer **7**. Dilution with ether of a methylene chloride extract of the 0.8 g. of crude product gave only 17 mg. of solid, m.p. 92–102°; this solid initially was soluble in chloroform, but after 2 days it dissolved only to the extent of about 33%. Only 8 mg. remained in the methylene chloride extract. The residue from the extraction was soluble only in dimethylformamide and therefore presumably was polymeric; it undergoes further polymerization because it precipitates from boiling dimethylformamide solution as material closely resembling **7**. The ether solution, containing the remaining reaction products, gave on evaporation 0.2 g. of oil; 70 mg. of solid, m.p. 65–70°, was isolated from the oil, but could not be purified (initially soluble in chloroform, but sparingly so after 2 days).

To test the possibility that the prolonged heating period (5 days) might have led to polymerization of lactam **2**, the oxidation was repeated with an influx time of 9 hr. for **12**, but with no greater success. In summary, all products seemed either to be high polymers of the lactam, insoluble even in hot dimethylformamide, or to be lower polymers which polymerized further with great ease.

Two attempts using iodine as oxidant led to polymers similar to those described above; *i.e.*, the products melted over broad ranges and were less than 10% soluble in common organic solvents, soluble fractions becoming less so upon standing.

In an effort to effect cyclization *via* a monothiolsulfonate, a solution of the dithiol (1 g.) in chloroform (200 ml.) containing pyridine (0.38 ml.) was added slowly (7 hr.) to a solution of *p*-toluenesulfonyl chloride (1 g.) in chloroform (600 ml.). After 24 hr. more, evaporation below 25° left oil, which was rubbed under ether and water; the yield of white solid was 1 g. (101%), m.p. *ca.* 52–58°; the infrared spectrum was identical with that of **7**. This product was more soluble than any previously encountered but could not be purified. Solutions became turbid in a few hours and precipitated solid; thin layer chromatography gave much tailing rather than well-defined spots and indicated heterogeneity. A toluene extract (30°) of the crude solid gave

(20) From *o*-benzylthiobenzoic acid,[21] according to W. J. Barry and I. L. Finar, *J. Chem. Soc.*, 138 (1954); yield 76%, m.p. 119–122° (lit.[20] m.p. 121–122°).

(21) H. A. Pitzsch, *Ber.*, **46**, 3102 (1913).

(22) Prepared according to E. Walton, A. N. Wilson, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, **76**, 1146 (1954).

(23) The reaction was carried out in a quartz vessel under nitrogen protected from light, with high dilution afforded by the apparatus of C. F. H. Allen and J. A. Van Allen, *J. Org. Chem.*, **14**, 754 (1949).

solid (6% over-all yield), m.p. 123–126°, but having mol. wt. 566. A methylene chloride extract of the crude product gave solid (12% over-all yield), m.p. *ca.* 50°, but having mol. wt. 518.

m-(**2-Aminoethyldithio**)**benzoic Acid Hydrochloride** (**15**). **A. From 2-Aminoethyl 2-Aminoethanethiolsulfonate Dihydrochloride** (**3**).—A solution at 50° of *m*-mercaptobenzoic acid[24] (2.00 g.) in ethanol (12 ml.) was added slowly over 15 min. to a stirred solution at 0° of the thiolsulfonate **3** (3.34 g.)[2] in water (8 ml.). The mixture was stirred for 3 hr. and then was chilled. The solid (1.55 g.) was collected; the infrared spectrum indicated that it contained considerable taurine. Numerous recrystallizations of this solid and other crops using water, alcohol, and acetone finally resulted in 1.16 g. (34%) of white solid, m.p. 187–190°, still containing taurine. Several recrystallizations from ethanol (below 40°) yielded the hydrochloride **15** having constant m.p. 191–193°.

Anal. Calcd. for $C_9H_{12}ClNO_2S_2$: C, 40.67; H, 4.55; N, 5.27; S, 24.13. Found: C, 40.50; H, 4.46; N, 5.10; S, 24.29.

Attempts to obtain a crystalline zwitterion **13** from this salt failed. Neutralization with 1 equiv. of sodium hydroxide precipitated no solid from concentrated solution; freeze drying gave only gum which resisted crystallization.

B. From *m*-**Carboxyphenyl** *m*-**Carboxybenzenethiolsulfonate** (**16**).—Thiolsulfonate **16** (14.8 g., m.p. 210–211° dec., finely ground) was added with stirring to 375 ml. of ethanol at 55°. After the mixture had cooled to 22°, 2-mercaptoethylamine hydrochloride (3.96 g.) in ethanol (80 ml.) under nitrogen was added dropwise over 80 min. with stirring. After 1 hr. more of stirring, the solution was concentrated (25°) to 160 ml. Solid was removed and the filtrate was concentrated to 90 ml. Dilution with ether (550 ml.), chilling, and one recrystallization from ethanol–ether below 40° gave 6.16 g. (67%) of the hydrochloride **15**, m.p. 191–193°; the infrared spectrum was identical with that of pure **15** described in A.

p-(**2-Aminoethyldithio**)**benzoic Acid** (**14**).—A mixture (9.0 g. of 4,4′-dithiodibenzoic acid, containing 30% (iodine titer) of *p*-mercaptobenzoic acid (0.018 mole),[25] and ethanol (50 ml.) was added rapidly to a stirred solution of the aminothiolsulfonate **3** (5.0 g.)[2] in water (25 ml.). After a stirring period of 1 hr., the mixture was centrifuged, then filtered. The filtrate was concentrated below 40° to about 15 ml., diluted with water (65 ml.), and extracted with two 200-ml. portions of ether. Ether then was placed in contact with the aqueous phase and a cold solution of potassium hydroxide (1.0 g.) in water (25 ml.) was added slowly with shaking. Concentration of the aqueous phase below 40° left an oil which crystallized upon standing for 6 weeks at *ca.* 25°. Trituration of the mass under cold water gave solid (2.2 g., 55%), m.p. 180–185° dec. Recrystallizations from vigorously boiling water gave **14**, m.p. 200–202° dec.

Anal. Calcd. for $C_9H_{11}NO_2S_2$: C, 47.15; H, 4.84; N, 6.11; S, 27.98. Found: C, 47.06; H, 4.83; N, 6.15; S, 27.95.

Dissolution of the acid **14** in 0.1 *N* hydrochloric acid followed by freeze drying gave the hydrochloride salt (**17**), m.p. 260°; the salt **17** also rapidly precipitated as needles after the acid **14** had been dissolved in 10% hydrochloric acid.

o-(**2-***n*-**Decylaminoethyldithio**)**benzoic Acid** (**20**).—One equivalent (46.0 ml.) of a standard solution (1.0 *N*) prepared by mixing concentrated hydrochloric acid and ethanol was added to a solution of 2-*n*-decylaminoethanethiol (9.90 g.) in ethanol (22 ml.). The resulting mixture immediately was added to a solution of crude *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate (15.50 g.) in ethanol (135 ml.).

After 20 min. at *ca.* 25°, the solution was evaporated (below 40°) to remove solvent. The residue, in ether (180 ml.) and water (135 ml.), was shaken vigorously while a cold solution of sodium hydroxide (3.68 g.) in water (120 ml.) was added.

An emulsion containing **20** resulted. Additional ether (*ca.* 600 ml.) was added slowly with scratching to initiate crystallization. At about 0°, the zwitterion **20** was obtained by filtration as white crystalline solid (15.40 g., 92%, m.p. 157–161°). Recrystallization from 1-butanol gave **20** identical (mixture melting point and infrared spectrum) with an analytical sample prepared on a smaller scale and recrystallized from 1-butanol and chloroform–ether to constant m.p. 161–162°. The product was soluble in alcoholic acid or base, but not in aqueous ethanol alone, and hence was amphoteric.

Anal. Calcd. for $C_{19}H_{31}NO_2S_2$: C, 61.75; H, 8.46; N, 3.79; S, 17.35. Found: C, 61.54; H, 8.41; N, 3.64; S, 17.60.

Disproportionation of Unsymmetrical Disulfides.—Approximately 1 mmole of disulfide was made to exactly 0.1 *M* in water (ethanol for disulfides **5** and **18**) and was heated in a sealed ampoule at 100° for 3 or for 22 hr. by suspension in vapors of refluxing water. The products from the hydrochloride salts gave precipitates directly; the products from the zwitterions gave precipitates only after acidification. After being heated, the samples were kept overnight at *ca.* 4°. Solid then was removed by filtration either directly (amine hydrochlorides), or after acidification (zwitterions) with 1 equiv. of hydrochloric acid. For the two water-insoluble disulfides (**5** and **18**) the water-soluble N,N′-diacetylcystamine was determined after evaporation of the ethanol, partitioning of the residue between water and ether, and evaporation of the separated water layer (in which the aromatic disulfide was virtually insoluble). After isolation, all solid symmetrical disulfides were dried to constant weight and were identified by their infrared spectra. When the "per cent disproportionated" was below 10, the initial unsymmetrical disulfides were recovered and shown to be essentially unchanged (mixture melting point and infrared spectra).

(24) Prepared by reducing the disulfide mentioned above with zinc dust in glacial acetic acid under nitrogen according to a recent procedure for the *para* analog[15]: yield 97%, m.p. 140–143° (lit.[15] m.p. 146–147°).

(25) Crude reaction product prepared according to the method of Campaigne and Meyer[15]; the content of the thiol could not be easily increased.

Synthesis of Laurolenic Acid

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The structure of laurolenic acid (**2**), one of the products which results from treatment of α-bromocamphoric anhydride with sodium carbonate, has been confirmed by synthesis of its racemic form. The synthesis proceeds by methylation of 2-carbomethoxycyclopentanone (**5**), methanolysis of the product **6** to dimethyl α-methyladipate (**7**), Dieckmann cyclization to 5-methyl-2-carbomethoxycyclopentanone (**8**), and methylation to the 2,5-dimethyl derivative **9**. These steps could be carried out starting with dimethyl adipate (**4**) without isolation of intermediates **5**, **6**, **7**, or **8**, 80% of the dimethyl keto ester **9** being obtained. Addition of the methyl Grignard reagent to **9**, dehydration, and hydrolysis completes the synthesis.

Laurolenic acid (1,2,3-trimethylcyclopent-2-ene carboxylic acid, **2**, described in the older literature as lauronolic acid) is a molecular rearrangement product derivable from camphoric acid by treatment of the corresponding bromo anhydride **1** with sodium carbonate[2] or by distillation of camphanic acid (**3**).[3] These reactions, particularly the former, played a complicating role in the classic structure determination of camphor,

(1) (a) U. S. Government Grantee, 1960–1962, administered by the Institute of International Education. (b) Texaco Undergraduate Scholar, 1960–1961; National Science Foundation Undergraduate Research Participant, 1961.

(2) O. Aschan, *Ber.*, **27**, 2112, 3504 (1894).

(3) R. Fittig and L. Woringer, *Ann.*, **227**, 1 (1885).