Organic Disulfides and Related Substances. XVII.[1a] Analogs of *o*-(2-Aminoethyldithio)benzoic Acid as Antiradiation Drugs[1b]

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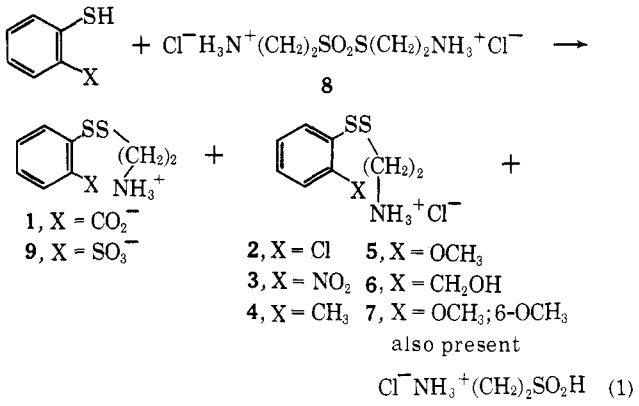
Analogs of *o*-(2-aminoethyldithio)benzoic acid (**1**), an active antiradiation drug, are reported. They were prepared by thioalkylating thiols with thiolsulfonates. Activity was not confined to a zwitterionic structure typified by acid **1**, since replacement of CO_2H by Cl, CH_3O, or $HOCH_2$ gave active compounds, but the most promising analogs were zwitterions in which the HO_2C of **1** was replaced by HO_3S (**9**) or the 2-aminoethyl moiety by 2-pyridylmethyl (**12**); both **9** and **12** were rated "good." Resistance of the unsymmetrical disulfides prepared to disproportionation into symmetrical ones differed for thermally and photochemically induced reactions. The *ortho* substituents had marked but unpredictable effects. No clear-cut relationships emerged of the three factors: resistance to disproportionation, antiradiation activity, and nature of the substituent.

o-(2-Aminoethyldithio)benzoic acid (**1**) gives good protection against lethal effects of ionizing radiation, but several derivatives or isomers of **1** do not (*e.g.*, the ester, the N-acetyl and N-(*n*-decyl)amino derivatives, and the *meta* or *para* isomers of **1**).[2] Synthesis



(1)

of *ortho*-substituted analogs of the presumed zwitterion **1** in which the carboxyl group was replaced by other groups was of interest for several reasons. (1) The possibility that analogs might be worthwhile protective agents was attractive. If activity were not confined specifically to the *ortho*-zwitterionic structure, it might be usefully correlated with electronic, steric, or anchimeric effects of *ortho* substituents. (2) A characteristic reaction of unsymmetrical disulfides is disproportionation to two symmetrical ones, as shown by eq 2. Ther-

$$2RSSR' \rightleftharpoons RSSR + R'SSR' \quad (2)$$

mally induced disproportionation of *para*-substituted unsymmetrical disulfides resembling **2–6** apparently followed first-order kinetics and gave a Hammett $\sigma-\rho$ correlation; the effect of substituents essentially reversed when disproportionation was induced by light.[3] It was desirable to learn whether correlations could be developed in the *ortho* series between three factors: nature of substituents, resistance to disproportionation, and activity as antiradiation drugs. (3) Perhaps one of the two sulfur atoms of the unsymmetrical aryl disulfides could be selectively oxidized, for reasons outlined in earlier work.[4]

Compounds **2–6** were prepared to provide a range of electron-withdrawing and electron-donating substituents in the *ortho* position. Their properties are reported in Table I. When the 2-methoxy compound (**5**) proved to be one of the more active antiradiation drugs of the series (*cf.* Table II), the 2,6-dimethoxy compound (**7**) was prepared to assess the radioprotective effect of a second flanking group; as Table II shows, however, it was inactive. Compounds **2–7** were prepared by the general method outlined in eq 1, *i.e.*, by thioalkylation of the corresponding aromatic thiols by means of 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (**8**). Preparation of a compound like **2–7** but with X = NH_2 was unsuccessful; reaction of *o*-aminobenzenethiol with **8** led quantitatively to *o*-aminophenyl disulfide, and the hydrochloride of the thiol led to an inseparable mixture. An attempt to prepare a compound with X = OH also was unpromising, apparently because the amphoteric product could not be isolated as usual.

Isolation of products **2–7** was best achieved by extraction of unreacted thiols with organic solvents after the reaction, followed by neutralization, extraction of free bases, and subsequent reconversion of the bases to the hydrochlorides. Since an early effort to recrystallize **4** from alcohol failed (rapid disproportionation), no further attempt was made to recrystallize compounds **2–7**. To obtain analytically pure samples, the unsymmetrical disulfide hydrochlorides were washed well with acetone. Evidence of purity was that products **2–7** showed a single spot in thin layer chromatography and no haziness upon dissolution in water (presence of 0.5% of phenyl disulfide in 2-(aminoethyldithio)benzene hydrochloride (**10**) was shown to cause haziness of an aqueous solution).

Conversions of the thiols to the products shown in Table I were rather low (21–42%) because of incomplete reaction when bases were not used.[5] Thus ether extraction after the reaction, followed by titration with iodine, indicated that 57 and 44% of *o*-mercaptobenzyl

(1) (a) Paper XVI: L. Field and W. B. Lacefield, *J. Org. Chem.*, **31**, 599 (1966); (b) reported in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 4–9, 1965, Abstracts, p N 25.

(2) R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965).

(3) T. F. Parsons, Ph.D. Dissertation, Vanderbilt University, May 1964, to be published.

(4) L. Field, H. Härle, T. C. Owen, and A. Ferretti, *J. Org. Chem.*, **29**, 1632 (1964).

(5) *Cf.* T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *ibid.*, **30**, 1923 (1965).

TABLE I

o-$XC_6H_4SSCH_2CH_2NH_3^+Cl^-$

No.	X	Conversion (yield), %[a]	Mp, °C[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % S	Found, % C	Found, % H	Found, % Cl	Found, % S
2	Cl	27	142–143	$C_8H_{11}Cl_2NS_2$	37.50	4.33	27.68	25.03	37.41	4.60	27.82	25.15
3	NO_2	41	190–192 dec	$C_8H_{11}ClN_2O_2S_2$[c]	36.02	4.16		24.04	35.89	4.15		24.15
4	CH_3	42	157–159	$C_9H_{14}ClNS_2$	45.84	5.98	15.04	27.20	45.65	6.09	15.19	27.24
5	OCH_3	22	142–143	$C_9H_{14}ClNOS_2$	42.93	5.60	14.08	25.47	43.01	5.62	14.51	25.56
6	CH_2OH	21(86)	153–155	$C_9H_{14}ClNOS_2$	42.93	5.60	14.08	25.47	43.05	5.71	14.18	25.29
7	2,6-$(OCH_3)_2$	40(81)	191–200 dec	$C_{10}H_{16}ClNO_2S_2$	42.61	5.72	12.59	22.75	42.42	5.73	12.73	22.47

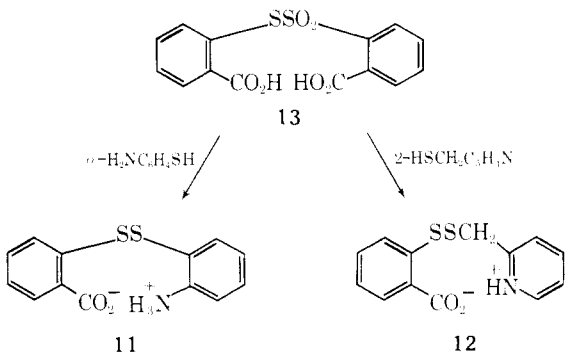
[a] "Conversion, %" is based on the amount of thiol taken; "yield, %" is based on that taken less the sum of that titrated by iodine and isolated as the symmetrical disulfide. [b] Melting point of the analytical sample. [c] *Anal.* Calcd: N, 10.50. Found: N, 10.47.

alcohol and 2,6-dimethoxythiophenol remained unchanged, respectively, in the preparation of **6** and **7**. For large-scale preparations, recovered thiols were employed again with thiolsulfonate **8**. In another experiment in the synthesis of **7**, the reaction was forced to completion by adding potassium hydroxide without extraction of unaltered thiol. The conversion of 40% dropped to only 14%, and the amount of 2,6-dimethoxyphenyl disulfide increased from 7 to 64%; perhaps the thiolate anion produced by the base attacked the unsymmetrical product in a chain-type reaction to result in symmetrical disulfide.

Interestingly, there was no by-product of disproportionation (o-nitrophenyl disulfide) isolated in the synthesis of **3**, even though nitro compound **3** underwent relatively rapid thermal disproportionation. This result was an early sign that although **3** proved to be thermally less stable than other disulfides it is more resistant to disproportionation induced by ambient light; a duality of disproportionation mechanism thus was indicated.

Compound **9** was obtained by reaction of the thiolsulfonate **8** with the o-mercaptobenzenesulfonate anion, in turn prepared by diazotization of orthanilic acid, reaction with potassium ethylxanthate, and saponification. The thiol was purified by precipitation of its lead thiolate and regeneration with hydrogen sulfide. An initial attempt to use the unpurified o-mercaptobenzenesulfonate from saponification of the unpurified xanthate gave the sulfonic acid zwitterion **9** (36%, mp 249–251°), but analytically pure **9** could not be obtained. Reaction of the purified thiol with the thiolsulfonate **8** resulted in precipitation of the zwitterion **9** (60% yield), which was purified by dissolution in alkali and reprecipitation with acid. **9** withstood recrystallization well, and the product had appropriate elemental analyses and neutralization equivalent (formol titration). Since elementary analyses did not distinguish **9** from the salt of the two symmetrical disulfides, its structure was confirmed in several ways. (1) It was not identical with cystamine 2,2′-dithiodibenzenesulfonate. The infrared spectrum of this salt was rather similar to that of the zwitterion **9**, except for changes in relative intensities, but the melting behavior was greatly different from that of **9**. (2) Vigorous oxidation of **9** gave taurine and dipotassium o-benzenedisulfonate, the identity of which was proved by comparison of infrared spectra with those of authentic substances; since the spectrum of the dipotassium salt was not highly characteristic, identity of X-ray diffraction patterns also was demonstrated. (3) Although the disulfide **9** proved to be one of the most resistant we have seen to disproportionation (its sparing solubility may be a factor), disproportionation could be accomplished by heating a solution of **9** at 100° for 7 days. The two symmetrical disulfides could not be readily separated, but cystamine could be isolated as its picrate without difficulty, consistent with at least 59% disproportionation, thus again substantiating the structure of **9**. That *no* picrate could be isolated after 25 hr at 68° and only one-half the above amount after 60 hr (see Table II) shows that the cystamine *must* have been formed by disproportionation and could not have been present originally.

In light of the good protective activity referred to below for the sulfonic acid **9**, two additional compounds (**11** and **12**) were synthesized which resemble **9** and **1** in having an *ortho* acidic function but which differ in the basic moiety of the unsymmetrical disulfide. Compounds **11** and **12** were prepared using the aryl arenethiolsulfonate **13**, as shown by eq 3.



Reaction of o-carboxyphenyl o-carboxybenzenethiolsulfonate (**13**) with o-aminobenzenethiol and 2-pyridinemethanethiol[6] resulted in precipitation of the desired zwitterions **11** and **12**, respectively. The thiolsulfonate **13** was not obtained easily from commercial 2,2′-dithiodibenzoic acid,[2] because of difficulties in purifying commercial disulfide by recrystallization. However, chlorinolysis of pure o-mercaptobenzoic acid afforded good thiolsulfonate **13** easily. This procedure has advantages over the original one based on the disulfide because of the relatively easy purification of o-mercaptobenzoic acid.

The infrared spectra of the unsymmetrical disulfides are not merely summations of the spectra of the sym-

(6) L. Nutting, R. M. Silverstein, and C. M. Himel, U. S. Patent 2,951,848 (1960); *Chem. Abstr.*, **55**, 4542 (1961).

TABLE II

DISPROPORTIONATION OF VARIOUS DISULFIDES AND PROTECTION AGAINST RADIATION[a]

No.	X	Disproportionation, %[b] Thermal (68°) 10 hr	25 hr	60 hr	Photochemical (25 min)[c]	Protection against radiation[d]	Drug dose, mg/kg	Vehicle of administration
7	2,6-$(OCH_3)_2$	83–89	82	97–100	14	0	50 or less	Saline soln
2	Cl	45[e]	85[e]	100[e]	45	+ or ++	50 or less	Saline soln
3	NO_2	21	53–56	100	0	0	51–150	Saline soln
10	H[f]	8	45	47	53	0	50 or less	Saline soln
5	OCH_3	8	36	66	37	+++	351–750	Soln in H_2O, pH 6.15
6	CH_2OH	10	35	41	24	+++	151–350	Saline soln, pH 5.95
4	CH_3	7	35	51	50	0	50 or less	Saline soln
9	SO_3H	...	<7	28	0	++++[g]	50 or less	Susp CMC–Tw
11	See text					0	51–150	Susp CMC–Tw
12	See text					++++	351–750	Susp CMC–Tw

[a] For general procedures, meanings of activity ratings, etc., see ref 8. CMC–Tw refers to a suspension in physiological saline solution containing methylcellulose and Tween 180.[8] [b] Calculated as (100 × 2 × moles of aromatic symmetrical disulfide isolated)/moles of unsymmetrical disulfide used.[15] [c] Photochemical disproportionation was performed twice: (1) with **2–6**, and **10** as a standard (53%); (2) with **7** and **9**, and **10** as a standard (95%). [d] 0 = none, + or ++ = some, +++ = fair, ++++ = good. [e] In 3 hr, 26%; in 40 hr, 88%. [f] Prepared by Parsons.[3] [g] The carboxylic analog was rated good (++++) at a dose of 151–350 mg/kg administered as a suspension in CMC–Tw.

metrical ones. In many instances, bands present in the symmetrical disulfides are absent in the unsymmetrical materials. Band shifts and new bands also often occur. Such behavior has been noted in our earlier work (*e.g.*, *cf.* ref 2).

It is well known that unsymmetrical disulfides disproportionate to equilibrium mixtures of unsymmetrical and symmetrical disulfides, and that equilibrium may be approached from either direction, as shown by eq 2.[7] However, this was believed not to be true in water as a solvent for our unsymmetrical disulfides containing one arylthio and one 2-aminoethylthio hydrochloride moiety. Rather, disproportionation has been assumed to proceed to completion irreversibly because of the virtual insolubility of the symmetrical aryl disulfides. This supposition was confirmed by heating cystamine dihydrochloride with three typical aryl disulfides under the usual conditions of disproportionation described below; all three aryl disulfides were recovered quantitatively and unchanged.

The disproportionation was carried out both thermally and photochemically to compare the reactivity of the *ortho*-substituted disulfides **2–7** and **9**. Results are shown in Table II, including those with the phenyl compound (**10**). The effect of substituents in conferring resistance to thermal disproportionation differed from that of the *para* series (for the *para* series, resistance increased in the order: $NO_2 < Cl < H < CH_3 < CH_3O$).[3] Attempts were made to plot concentration of unreacted unsymmetrical disulfide *vs.* time (zero order), log concentration *vs.* time (first order), and the reciprocal of concentration *vs.* time (second order). Unlike the *para* series, which was first order in unconsumed unsymmetrical disulfide,[3] no linearity in the plot was discernible in any instance. Table II reveals that the relative ease of disproportionation for the disulfides depends on the time of reaction, as summarized below for the order of increasing resistance to disproportionation.

(a) 10 hr: 2,6-$(OCH_3)_2 < Cl < NO_2 < CH_2OH \sim H \sim OCH_3 \sim CH_3$

(b) 25 hr: 2,6-$(OCH_3)_2 \sim Cl < NO_2 < H < OCH_3 \sim CH_2OH \sim CH_3 < SO_3H$

(c) 60 hr: 2,6-$(OCH_3)_2 \sim Cl \sim NO_2 < OCH_3 < CH_3 \sim H < CH_2OH < SO_3H$

Remarkable thermal instability was noticed when a second methoxyl group was introduced in the 6-position of the benzene nucleus of disulfide **5**, giving the 2,6-dimethoxyphenyl compound **7**. It seems likely that this instability of **7** arises from a noncoplanarity of the ring with the two sulfur atoms which is unique to **7**.

Since little if any disproportionation was observed for the zwitterionic disulfide **9** after 25 hr and only 28% after 60 hr, great thermal stability seems to be associated with zwitterionic character (the zwitterion **1** and its isomers seemed more stable than their hydrochloride or sodium salts[2]). Despite the stability and sparing solubility of **9**, it could not be obtained by prolonged standing of a solution of disodium 2,2′-dithiodibenzenesulfonate and 2-mercaptoethylamine hydrochloride in a minimum of water; presumably attack of the thiol on the disulfide is very sluggish.

Thin layer chromatography after thermal disproportionation of the phenyl compound **10** showed that the reaction is a clean one without much complication. Only three components were found: phenyl disulfide, cystamine dihydrochloride, and **10**. Furthermore, a good material balance accorded well with eq 2.

Results of light-induced disproportionation of the *ortho*-substituted disulfides are shown in Table II and can be summarized in the following order of increasing resistance: $H \sim CH_3 < Cl < OCH_3 < CH_2OH <$ 2,6-$(OCH_3)_2 < NO_2 \sim SO_3H$. This order differs from either that obtained for the *para* series ($H < CH_3 \sim CH_3O < Cl < NO_2$),[3] or those obtained in thermal disproportionation. It was surprising that the thermally least stable **7** was quite resistant to photochemical disproportionation.

No clear-cut generalizations as to effects of substituents on relative resistance emerge either in the

(7) (a) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951); (b) S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Petrol.*, **39**, 206 (1953); (c) L. Haraldson, C. J. Olander, S. Sunner, and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960); (d) G. Dalman, J. McDermed, and G. Gorin, *J. Org. Chem.*, **29**, 1480 (1964).

ortho series or in its relation to the *para* series, except that in thermal disproportionation the zwitterionic structure of **9** confers stability and the two *ortho* substituents of **7** confer unexpectedly great instability: however, there does appear to be a trend in the thermal disproportionations for electron-withdrawing substituents to decrease stability (*cf.* **2** and **3** in Table II).

In efforts to oxidize unsymmetrical disulfides selectively to one thiolsulfonate, the *o*-nitro and *o*-methoxy compounds were chosen as typifying opposite extremes. Use of the nitro disulfide **3** under the usual conditions[4] with hydrogen peroxide led to recovery of 82% of **3**, along with taurine (20%) and *o*-nitrophenyl disulfide (19%). The *o*-methoxy disulfide **5** gave taurine (16%), the symmetrical aminoethyl thiolsulfonate **8** (47%), and a material which contained no nitrogen and was presumed to be the other possible symmetrical thiolsulfonate (*i.e.*, *o*-methoxyphenyl *o*-methoxybenzenethiolsulfonate, 65%). Since formation of symmetrical compounds and oxidation to taurine seemed to predominate, prospects for synthetically useful selective oxidations seemed bleak.

Protective activities were kindly determined under the auspices of Drs. D. P. Jacobus, T. R. Sweeney, and P. Coad at the Walter Reed Army Institute of Research, Washington, D. C. General procedures and the meaning of activity ratings were described previously.[8] Results in Table II show that the presumably zwitterionic compounds **9** and **12** resemble the original one (**1**) in having "good" activity; three of the nonzwitterionic *ortho* analogs are active, but none is better than "fair." There are no striking correlations between protective activities and either electronic effects of the *ortho* substituents or resistance of the disulfides to disproportionation. Nevertheless, the *ortho* substituent obviously plays a highly significant role, even though an unpredictable one, in both protective activity and resistance to thermally or photochemically induced disproportionation.

Experimental Section[9]

Starting Materials.—*o*-Toluenethiol and orthanilic acid were purchased. *o*-Chlorothiophenol,[10] thioguaiacol,[11] *o*-mercaptobenzyl alcohol,[12] *o*-nitrothiophenol,[13] and 2,6-dimethoxythiophenol[14] were prepared according to known procedures. The thiolsulfonate **8** was partially supplied through the kindness of Dr. T. R. Sweeney (prepared by Distillation Products Industries) and partially prepared according to an earlier procedure.[15]

2,6-Dimethoxyphenyl disulfide was prepared as a derivative by titration of 2,6-dimethoxythiophenol[14] (0.48 g) in 50 ml of ether against 0.1 *N* I_2-KI solution to an I_2 end point. The white precipitate was collected, washed with ether, and dried: yield, 0.36 g (75%); mp 188–194°. Recrystallization from 1:1 $CHCl_3$–petroleum ether gave 0.30 g (63%) of the disulfide, mp 199–201°.

Anal. Calcd for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.36. Found: C, 56.96; H, 5.52.

General Procedure for Preparation of the Unsymmetrical Disulfides 2–7.—*ortho*-Substituted aromatic thiols (0.025 mole) and 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (**8**, 0.025 mole) were stirred for 0.5 hr in water (15 ml) mixed with ethanol (40 ml for **2**, **4**, and **5**; 60 ml for **6**; and 80 ml for **3** and **7**). Evaporation below 30° within 1 hr gave a white residue, which was dissolved in 15–125 ml of water and extracted with 100 ml of ether for **2** and **4**–**7**, or a mixture of benzene–ether (1:1) for **3**, to remove unchanged thiols; the extracts were titrated with iodine solution for assay of thiol, where appropriate. The aqueous layer then was shaken with 40 ml of solvent (hexane for **2** and **4**; a mixture of C_6H_6–hexane for **3** (1:1) and **5** (1:2); C_6H_6–ether (1:1) for **7**; and C_6H_6 for **6**), while 25 ml of an iced aqueous solution of KOH (4.8 g) was added. The water layer was extracted twice more with the solvent described above (20 ml portions). Each organic layer was backwashed rapidly with water, and after filtration was shaken at once with the same portion of 2.5 ml of 12 *N* HCl in 25 ml of water cooled in an ice bath. The extraction was effected within 0.5 hr. Precipitation occurred immediately upon contact with the acid. With **6**, the three organic layers were filtered without backwashing with water[16] and were shaken at once with the required amount of HCl; precipitation was much enhanced by more acid (7.5 ml instead of 2.5 ml). The crude products **2**–**7** were separated by filtration, dried under reduced pressure for 2 hr, and washed several times with acetone thoroughly. The organic raffinate was washed, dried, and evaporated to give the symmetrical aryl disulfide (identified by infrared spectrum and/or melting point). Results are shown in Table I.

Thin layer chromatograms of the unsymmetrical disulfides (**2**–**7**) on Eastman Chromagram sheet (Type K 301 R) developed with 95% ethanol at room temperature showed only single spots after exposure to I_2 vapor (R_f 0.71, except for **3** which had R_f 0.53).

***o*-(2-Aminoethyldithio)benzenesulfonic Acid (9). A. Preparation.**—The general procedure for diazotization of orthanilic acid was that of Stephens[17]; the diazotization was found not to proceed, however, if chilling is done much below 0°. Finely pulverized orthanilic acid (173.2 g, 1 mole) was suspended in 350 ml of concentrated HCl along with 800 ml of water and was heated for a short time. After being cooled to room temperature, the suspension was stirred quite rapidly while a cold solution of $NaNO_2$ (73.2 g, 1.06 moles) in 110 ml of water was added at *ca.* 0° during 1 hr. A positive starch–iodide test for nitrite ion still resulted after *ca.* 20 min. The reaction mixture was stirred 50 min more at 0° and then a white diazonium salt (170.0 g, wet weight) was removed by filtration; this salt gave a deep red precipitate after reaction with β-naphthol in NaOH solution. The diazonium salt thus prepared was added gradually with good stirring in small portions to potassium ethylxanthate (240.3 g, 1.5 moles) in 1 l. of water heated at *ca.* 70° during 1 hr. Vigorous evolution of nitrogen occurred with each addition. After evaporation of the reaction mixture to 250 ml, NaOH (80.0 g, 2 moles) in 200 ml of water was added and the mixture was heated under reflux overnight. After being cooled in an ice bath, it was acidified with 190 ml of concentrated HCl in 50 ml of ice–water (to *ca.* pH 3).[18]

When the aqueous solution of the *o*-mercaptobenzenesulfonate was immediately added to a boiling alcoholic solution of lead acetate trihydrate (189.7 g, 0.5 mole) in 1.6 l. of ethanol, precipitation occurred upon cooling. The resulting orange precipitate was separated by filtration and was washed with ethanol and water and dried in air (yield 280.0 g). The lead mercaptide (84.0 g) was suspended in 500 ml of water through which H_2S

(8) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(9) Melting points are corrected. They were determined in a capillary tube using an ASTM-specification thermometer. 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 were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137B or Beckman Model IR10 spectrophotometer with films of liquids and Nujol mulls or KBr pellets of solids; in reported absorptions, "b" signifies broad. X-Ray diffraction patterns were determined by Crobaugh Laboratories, Cleveland, Ohio. Evaporation of solvents usually was done under reduced pressure using a rotary evaporator.

(10) G. Daccomo, *Jahresbericht* (1), 1377 (1891).

(11) F. Mauthner, *Ber.*, **39**, 1348 (1905).

(12) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1952 (1963).

(13) D. G. Foster and E. E. Reid, *J. Am. Chem. Soc.*, **46**, 1937 (1924).

(14) V. Baliah and T. Rangarajan, *J. Indian Chem. Soc.*, **38**, 33 (1961). We obtained 2,6-dimethoxythiophenol in 79% yield by fractional distillation: bp 125–128° (3.3 mm). Several recrystallizations from ether gave material having an iodine titer of 93% and mp 82–84°; lit.[14] mp 85–86°.

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

(16) An attempt was made to backwash the organic layer with water as usual, but, for some reason, it produced an unidentified white substance insoluble both in organic solvents and in water or acid.

(17) W. D. Stephens, Ph.D. Dissertation, Vanderbilt University, 1960, pp 37–38.

(18) It was found that at pH 7 the lead salt described below became a black mass.

was bubbled until no more precipitation of PbS occurred. After *ca.* 20 min, the mixture was filtered and the filtrate was freed from excess H_2S under reduced pressure. The filtrate decolorized aqueous I_2–KI solution rapidly.[19] The thiolsulfonate **8** (51.4 g, 0.2 mole) in 100 ml of water was added with stirring to the filtrate prepared above. After 20 min, precipitation of white solid began. Stirring was continued overnight. Filtration gave 28.5 g of **9** (54%; yields are based on the assumption of **8** as the limiting reagent). More deposited after 1 week, making a total yield of 31.6 g (60%).

The product **9** was purified by dissolving 31.6 g (0.12 mole) in 30 ml of water containing 4.8 g (0.12 mole) of NaOH, followed by acidification with 12 ml of cold concentrated HCl and chilling; 27.8 g (88%) was recovered; yield, 52%; mp 238–242°. Several recrystallizations from water (100°) gave material of constant mp 254–256° (clear melt, no decomposition). The infrared spectrum showed the following medium-to-strong absorptions (KBr pellets, cm^{-1}): 3450 b, 3100–2910 b, 2900–2600 b, 1615, 1495, 1445, 1425, 1200 b, 1135, 1100, 1060, 1010, 752, 740, 665, 610, and 570.

Anal. Calcd for $C_8H_{11}NO_3S_3$: C, 36.20; H, 4.18; N, 5.28; S, 36.25; neut equiv, 265. Found: C, 36.07; H, 3.98; N, 5.32; S, 35.98; neut equiv (formol), 269.

B. Cystamine 2,2′-Dithiodibenzenesulfonate.—2,2′-Dithiodibenzenesulfonate anion was prepared as follows. The filtrate containing the *o*-mercaptobenzenesulfonate, prepared from the lead mercaptide (28.0 g) and H_2S as described, was cooled in an ice bath and 30% H_2O_2 (6 ml) was added slowly until a positive starch–iodide test resulted. The reaction mixture was allowed to stir overnight. After evaporation almost to dryness, the residue was triturated with 150 ml of absolute alcohol to obtain a hygroscopic solid; yield, 8.9 g. A solution of cystamine dihydrochloride (0.14 g, 0.6 mmole) in water (0.2 ml) was added to a stirred solution of the 2,2′-dithiodibenzenesulfonate product (0.25 g, 0.6 mmole estimated) in water (1 ml). Chilling followed by filtration gave the title compound (0.20 g, *ca.* 63%), mp 214 (began to darken) to 241° (dec complete); the infrared spectrum was similar to that of **9**; however, there were significant differences in relative intensities of bands. The mixture melting point with **9** was 214–237° dec and obviously differed from the melting behavior of **9**.

C. Oxidation of 9.—Disulfide **9** (2.7 g, 10 mmoles) was dissolved in 20 ml of warm water, and 8 ml of 30% H_2O_2 was added in small portions during 1.5 hr until a positive starch–iodide test resulted. The mixture then was heated under reflux overnight. The starch–iodide test then was negative. After evaporation to a total volume of *ca.* 10 ml at 40°, followed by addition of 50 ml of absolute alcohol and chilling for 24 hr, 0.92 g (72%) of taurine was obtained. After several thorough washes with absolute alcohol and drying in air, the infrared spectrum was identical with that of authentic taurine. The filtrate was neutralized with KOH and evaporated to dryness, and the residue was triturated with 10 ml of absolute alcohol to obtain 3.57 g of white dipotassium *o*-benzenedisulfonate. Recrystallization from 85% alcohol gave pure substance; yield, 3.16 g (99%). The infrared spectrum was identical with that of authentic dipotassium *o*-benzenedisulfonate.[20] The X-ray diffraction patterns showed that the salt obtained by oxidation of **9** was identical with the authentic sample,[20] although there were some differences in the minor patterns.

D. Disproportionation for Structural Proof of 9.—The zwitterionic disulfide **9** (265.2 mg) was suspended in 10 ml of water in an ampoule, which was sealed immediately, wrapped with foil, immersed in boiling water (**9** dissolved), and heated continuously for 7 days. Evaporation gave a residue, which had the melting point behavior of the cystamine salt described under B, rather than of **9**. The residue was dissolved in water (5 ml) and then was boiled a few minutes with a saturated solution of picric acid in alcohol (5 ml). Chilling and filtration gave crude cystamine picrate which weighed 388.8 mg (127%), mp 190–197°. After recrystallization from 75% alcohol, 135.0 mg (44%)[21] was obtained pure; the melting point and mixture melting point were 201–203°. The infrared spectra of the isolated and authentic picrates were identical.

***o*-(2-Aminophenyldithio)benzoic Acid (11).**—*o*-Aminobenzenethiol (2.63 g, 0.021 mole) and thiolsulfonate **13** (6.43 g, 0.019 mole) in ethanol (50 ml) were stirred at room temperature for 3 hr. Precipitation occurred immediately. After 3 hr, filtration gave 3.55 g of a white solid (67%), mp 167° dec. The crude solid was dissolved in 350 ml of absolute alcohol at room temperature and was treated once with Darco. Water (450 ml) was added until the cloudiness point was reached, and the mixture was chilled at *ca.* 0–5° for 1 hr and filtered. Several recrystallizations gave white solid; yield of **11**, 2.7 g (51%); mp 167–169° dec.

Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.29; H, 4.00; N, 5.05; S, 23.12. Found: C, 56.37; H, 4.00; N, 5.14; S, 23.05.

***o*-(2-Pyridylmethyldithio)benzoic Acid (12).**—Exactly in the same manner described for **11**, a white solid precipitate (11.0 g, 109%) immediately resulted from 2-pyridinemethanethiol (5.0 g, 0.040 mole)[6] and **13** (12.3 g, 0.036 mole). Several recrystallizations from methanol gave **12**; yield, 7.3 g (72%); mp 176–178° dec.

Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.29; H, 4.00; N, 5.05; S, 23.12. Found: C, 56.14; H, 3.97; N, 5.15; S, 23.20.

The infrared spectrum showed medium-to-strong absorptions (KBr pellet, cm^{-1}) at 3448 b, 1695, 1600, 1460, 1433, 1316, 1087, 1020, 806, 785, 758, 746, and 692.

***o*-Carboxyphenyl *o*-Carboxybenzenethiolsulfonate (13).**—In a modification of our earlier procedure,[2] chlorine (20.9 g, 13.5 ml) was introduced slowly (45 min) into a stirred mixture at 0–5° of *o*-mercaptobenzoic acid (30.2 g, 0.196 mole; recrystallized from ethanol and dried to constant weight under reduced pressure) and acetic acid (5.6 ml) in previously distilled methylene chloride (110 ml). Within 10 min, the mixture became amorphous. It was stirred 10 min more at 0°, after which water (3.6 ml) was added slowly with vigorous stirring. The suspension was kept at *ca.* 20 mm for 4 hr. Solid then was triturated twice under cold water (250 ml). Collection by filtration gave 30.0 g of solid, which was triturated with 300 ml of 95% ethanol. The filtrate was evaporated to dryness, and the residue was triturated with cold water (200 ml); yield of **13**, 20.0 g (60%); mp 215–223° dec (lit.[2] mp 218–222° dec). The infrared spectrum was identical with that of authentic **13**.[2]

Thermal Disproportionation of Unsymmetrical Disulfides. A.—Unsymmetrical disulfides (1 mmole) were dissolved (**2–7**) or suspended (**9**) in 10 ml of water in 50-ml flasks; the flasks were wrapped with Al foil, immersed to their necks in a thermostated oil bath, and heated at 68° for the designated time intervals. The flasks then were withdrawn and chilled in ice. The contents (except with **9**) were extracted twice ($CHCl_3$ 10 ml), and the extracts were washed with water, dried, and evaporated to a residue, which was kept under reduced pressure until the weight was constant. The symmetrical aryl disulfides thus obtained were characterized by their infrared spectra and/or their melting point. "Disproportionation, %," was calculated as usual.[15]

In the case of **9**, 87% of unchanged material was recovered after 25 hr by filtration; it was identified by melting point (255°) and infrared spectrum; the filtrate gave no cystamine picrate at all when residue obtained by evaporation was dissolved in water (5 ml) and boiled with a saturated solution of picric acid in alcohol (5 ml).[22] After 60 hr, chilling gave no precipitate. Evaporation gave residue which was dissolved in water (5 ml) and boiled with a saturated solution of picrate acid in alcohol (5 ml). Crude picrate was recrystallized as usual (*cf.* ref 21); yield of cystamine picrate, 64.38 mg (21%); mp and mmp 205–206°. Based on the factor of 100/74 × 21,[21] disproportionation amounted at least to about 28%. A homogeneous aqueous solution of **9**, on the other hand, gave no picrate at all.

(19) During the course of our investigation *o*-mercaptobenzenesulfonic acid was reported (different synthesis) by A. E. Kretov, A. S. Bespalyi, and N. N. Politun, *Zh. Obshch. Khim.*, **34**, 2066 (1964); *Chem. Abstr.*, **61**, 8220 (1964).

(20) Purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis., and recrystallized.

(21) The cystamine picrate was recrystallized owing to the result of a blank run. When 74 mg of cystamine dihydrochloride was dissolved in 5 ml of water, boiled a few minutes with 5 ml of a saturated picric acid solution in alcohol, and chilled at *ca.* 0°, 304.0 mg of crude picrate was obtained (152%). After recrystallization from 75% alcohol, 148.4 mg remained (74%). The correction factor of 100/74 × 44, based on true and isolated amounts of cystamine in this identical control isolation, shows that picrate isolated in the experiment corresponds to disproportionation at least to the extent of about 59%.

(22) As a result of a blank run, it was learned that presence of as little as 19.5 mg of cystamine 2,2′-dithiodibenzenesulfonate in water (5 ml), corresponding to 7% disproportionation, was detectible by precipitation of cystamine picrate; hence the 25-hr result in Table II is reported as "<7."

B. Irreversibility of the Disproportionation.—Cystamine dihydrochloride (0.5 mmole) was heated with 0.5 mmole of phenyl disulfide, *o*-chlorophenyl disulfide, or *o*-hydroxymethylphenyl disulfide, as usual for disproportionation experiments, in 10 ml of water at 100° for 72 hr. The three aryl disulfides were recovered unchanged (mixture melting point and infrared spectrum) in yields of 99, 104, and 101%, respectively.

C. Material Balance in the Disproportionation of 2-Aminoethyldithiobenzene Hydrochloride (10).—An aqueous solution of **10** (0.2338 g, 1.054 mmoles) in water (10 ml) was heated at 68° exactly as in the disproportionation of **2–7**, except that a 10-day period was used to assure nearly complete reaction. Phenyl disulfide was extracted with $CHCl_3$; yield, 105.8 mg (92%); mp and mmp 58–59° (infrared spectrum identical with that of phenyl disulfide). Thin layer chromatography was performed on this solid, along with the aqueous phase and appropriate authentic samples, on Eastman Chromagram sheet (Type K 301R; previously activated at 110° for 0.5 hr). Development with 95% acetic acid for 2 hr and exposure to iodine vapor showed one spot with R_f 0.81 (identical with authentic phenyl disulfide) and only two other spots, with R_f values of 0.40 and 0.66 corresponding to the authentic samples of cystamine dihydrochloride and **10**, respectively.

The aqueous phase was evaporated under reduced pressure to a white residue. The residue was rubbed with cold absolute ethanol, which removed **10** but left most of the cystamine salt. Evaporation of the ethanol left crude **10**. Several applications of this procedure finally separated 29.6 mg (13%) of **10**, mp and mmp 127–131°, and 102.6 mg (86%) of cystamine dihydrochloride, mp and mmp 218–220° dec. Infrared spectra for **10** and the cystamine salt were identical with those of authentic material. Since thin layer chromatography showed that only three materials were present and since separation showed these materials to be the two symmetrical disulfides (86–92%) and unchanged **10** (13%, evidently still containing a little cystamine salt), the disproportionation must proceed rather cleanly with rather slight formation of by-products.

Photochemical Disproportionation of Disulfides 2–7 and 9.—Aqueous solutions of 1 mmole of unsymmetrical disulfide in 20 ml of water (0.05 *M*) in 50-ml Pyrex flasks[23] were irradiated at a distance of 12.5 cm with an ultraviolet source (100-w Hanovia ultraviolet lamp, Engelhard Industries Inc., Newark, N. J.) for 25 min at room temperature. Isolations and calculations were done in the same manner described for thermal disproportionation.

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(23) A homogeneous solution of sparingly soluble **9** was prepared by dissolving 1 mmole in 10 ml of hot water, cooling, and diluting with 10 ml more.

Nitrofuryl Heterocycles. I. 5,6-Dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazoles and Acid Addition Salts[1]

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The preparation of several 5,6-dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazoles and acid addition salts is reported and their *in vitro* antibacterial activity is discussed. These compounds are prepared by the condensation of bromomethyl and chloromethyl 5-nitro-2-furyl ketones with ethylenethiourea and C-alkyl-substituted ethylenethioureas. The acid-catalyzed condensation of 5-nitro-2-furaldehyde with chloroacetone produces 3-chloro-4-(5-nitro-2-furyl)-3-buten-2-one. Condensation of 5-nitro-2-furaldehyde with (3-chloro-2-oxopropylidene)triphenylphosphorane yields 1-chloro-4-(5-nitro-2-furyl)-3-buten-2-one which reacts with ethylenethiourea to give the vinylog of the title compound.

Since the introduction of nitrofurazone[2] as a topical antibacterial agent, other nitrofurans have been prepared in an effort to increase activity. This paper describes the synthesis of a new class of nitrofurans, the 5,6-dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazoles and their acid addition salts, which possess enhanced *in vitro* activity, especially against *Proteus vulgaris* and *Pseudomonas aeruginosa* organisms.

Chemistry.—The reaction of ethylenethiourea (**1a**) and *p*-nitrophenacyl bromide to yield 6,7-dihydro-3-(4-nitrophenyl)-5H-imidazo[2,1-*b*]thiazolium bromide was reported by Fefer and King.[3] When this reaction was applied to **1a** using bromomethyl and chloromethyl 5-nitro-2-furyl ketones (**2a**[4] and **2b**,[5] respectively) in refluxing ethanol, or dimethylformamide at steam bath temperature, the imidazothiazoles **3a** and **3b**, respectively, were formed. Neutralization of the salt **3** produced the free base **4** which could be converted to other salts. Because of the good *in vitro* activity of these compounds, several homologs were prepared.

Alkyl substitution on the imidazoline ring carbons was accomplished by using C-alkyl-substituted ethylenethioureas (**1**). The ethylenethioureas were prepared from the appropriately substituted ethylenediamines and carbon disulfide.[6,7] Condensation of these ethylenethioureas with **2a** or **2b** resulted in the products **3a–e** listed in Table I. It is interesting to note that the synthesis of **3c** and **3d**, as well as **3a** and **3b**, proceeded smoothly at steam bath temperature. However, in order to obtain **3e**, it was necessary to carry out the reaction in refluxing Methyl Cellosolve. Furthermore, it should be noted that the methyl and *gem*-dimethyl groups of **3c** and **3d**, respectively, can be on either methylene carbon of the imidazoline ring. Thin layer chromatography in several systems indicate

(1) Presented at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 11P.

(2) Furacin®, 5-nitro-2-furaldehyde semicarbazone.

(3) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).

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(5) G. Gever, U. S. Patent 3,111,530 (1963); *Chem. Abstr.*, **60**, 2893 (1964).

(6) A. F. McKay and W. G. Hatton, *J. Am. Chem. Soc.*, **78**, 1618 (1956).

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