temperature, the reactants were heated for 10 min. on a steam bath. The excess of thionyl chloride and ether was removed by evaporation under reduced pressure; final traces of thionyl chloride were removed by adding benzene and evaporating again.

To a solution of the residue in 90 ml. of sodium-dried benzene cooled to 2°, was added a solution of 30 ml. of stannic chloride in 30 ml. of benzene (sodium-dried) in two equal portions, the second portion being added after the reaction mixture had cooled down to 20°. Cooling was maintained during the whole period, and *ca.* 20 min. after the initial addition the reaction mixture was poured over a mixture of ice and concentrated hydrochloric acid. After 12 hr., the benzene layer was separated, combined with a benzene extract (100 ml.) of the aqueous layer, washed with sodium bicarbonate solution, then water, and dried (K_2CO_3). The yellow solid obtained on removal of the benzene crystallized from ethanol as yellow-green prisms, m.p. 108.5–110° [11] (18.9 g., 78%), ν_{max}^{CBr} 1650 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{13}H_{10}OS$: C, 72.86; H, 4.70; S, 14.96. Found: C, 73.32; H, 4.76; S, 14.96.

The compound formed a semicarbazone which crystallized from chloroform–ethanol as fine needles, m.p. 228.5–230°.

Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; S, 11.82. Found: C, 61.40; H, 5.22; S, 11.87.

Dihydronaphtho[1,2-*b*]-4H-thiapyran (XII). A. From Ring Closure of X.—A solution of 5.0 g. (0.012 mole)of X and 12.6 g. (0.10 g.-atom) of iodine in 450 ml. of ethylene glycol was heated under reflux for 8 hr. On cooling, the mixture was poured into 1.3 l. of water and the product was extracted with three 250-ml. portions of ether. The combined extracts were washed with dilute sodium bisulfite solution, followed by water, and dried (K_2CO_3). The dark red oil obtained on removal of the solvent was absorbed onto an alumina column (160 g.) and, on elution with a *n*-hexane–chloroform mixture (4:1), a yellow oil was obtained (1.58 g.) which distilled under reduced pressure giving 1.26 g. (25%) of an almost colorless distillate of XII, b.p. 138–142° (0.2 mm.). Vapor phase chromatography[33] indicated that the distillate was a single compound.

Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01. Found: C, 78.25; H, 6.14; S, 15.99.

Compound X (4.44 g., 0.011 mole) and iodine (2.82 g., 0.022 g.-atom) in ethylene glycol dimethyl ether (400 ml.) were heated under reflux (90°) for 8.5 hr. After removing the bulk of the solvent by evaporation under reduced pressure, 250 ml. of water was added and the product was extracted with three 80-ml. portions of ether. After washing the combined extracts with dilute sodium bisulfite solution, then sodium bicarbonate solution, followed by water and drying, removal of the solvent and distillation of the residue under reduced pressure afforded 2.2 g. (50%) of XII as a liquid, b.p. 159–163° (0.4 mm.). The infrared spectrum of the distillate was identical with that of XII above.

The residue (1.45 g.) from the distillation, after chromatography on alumina, gave a white solid, m.p. 60.5–62.5° (0.62 g.) and m.m.p. 60.5–63.5° with starting material, m.p. 61.5–63.5°.

B. By Reduction of XI.—A modification of the Wolff–Kishner reduction used in the naphthiapyrone series was applied with success in the present case.[12] Compound XI (10.0 g.) and hydrazine hydrate (6.4 ml. of 85% aqueous solution) were heated together in diethylene glycol (65 ml., redistilled) under reflux for 1 hr. Water and excess hydrazine were then distilled until the temperature reached 195°, whereupon the solution was cooled to 110° and 8.9 g. of potassium hydroxide was added. The mixture began to boil of its own accord, and heating was resumed. When the temperature again reached 190°, refluxing was continued for 4 hr. On cooling, the liquid was poured into 250 ml. of water and extraction with four 70-ml. portions of ether followed by combination of the extracts, washing with water, drying (K_2CO_3), and removal of the ether gave 7.64 g. (82%) of a yellow oil which distilled under reduced pressure in the range of 132–138° (0.15 mm.).

The infrared spectrum (liquid film) was identical with the spectrum of XII (above). The product formed a picrate and, on oxidation, a sulfone identical with those described below prepared from the product of ring closure of the disulfide X.

Dihydronaphtho[1,2-*b*]-4H-thiapyran Picrate.—Treatment of XII with an excess of a saturated ethanolic solution of picric acid gave a picrate which crystallized from ethanol as dark red needles, m.p. 128.5–130°.

Anal. Calcd. for $C_{19}H_{15}N_3O_7S$: C, 53.14; H, 3.52. Found: C, 53.52; H, 3.29.

Dihydronaphtho[1,2-*b*]-4H-thiapyran 1,1-Dioxide.—A solution of 0.3 g. of XII in 4 ml. of glacial acetic acid was treated with 1.5 ml. of 30% hydrogen peroxide and heated for 2 hr. on a steam bath. The cooled solution was poured onto ice (30 g.) and the product was collected by filtration, washed with water, and crystallized from methanol. Recrystallization yielded 0.15 g. of light yellow plates, m.p. 164.5–166.5°; ν_{max}^{KBr} 1112 (s) and 1277 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 67.59; H, 4.89; S, 13.74.

(33) Using an F and M Scientific Corp. Model 500 gas chromatograph.

Organic Disulfides and Related Substances. XI. Bisalkylidene, -alkylene, and -arylene Disulfides Containing 2-Aminoethyl Moieties[1]

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Syntheses and thermal stabilities in solution are reported for a number of bisdisulfides of the general formula RSSR′SSR, where R is a 2-aminoethyl moiety. Syntheses involved reaction of appropriate thiolsulfonates with alicyclic 1,1-dithiols, aromatic and aliphatic 1,2-dithiols, and aliphatic 1,4-dithiols. 1,1-Bisdisulfides are the least stable thermally of the series of bisdisulfides studied; *the cyclohexylidene bisdisulfide is remarkably less stable than its cyclopentylidene counterpart.* Aromatic 1,2-bisdisulfides are less stable than 1,2- and 1,4-aliphatic bisdisulfides; the latter gave 1,2-dithiacyclohexane in good yield upon decomposition. Typical free bases are much less stable than hydrochloride salts and typical amides are more stable.

An earlier paper[2] described syntheses of some unsymmetrical disulfides by reaction of thiosulfonates with thiols according to the previously reported but little used reaction,[3] $RSO_2SR + R'SH \rightarrow RSSR' + RSO_2H$. This paper reports extension of this method to the synthesis of bisdisulfides by reaction of 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (1) or 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (2) with alicyclic 1,1-dithiols, aliphatic 1,4- and 1,2-di-

(1) (a) 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. We are indebted to Drs. T. R. Sweeney and D. P. Jacobus of the Walter Reed Army Institute of Research, Washington, D. C., for certain materials and for evaluation of protection by products against lethal effects of radiation, which is now in progress. (b) Paper X: L. Field, T. F. Parsons, and R. R. Crenshaw, *J. Org. Chem.*, **29**, 918 (1964).

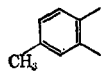
(2) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

(3) *Cf.* A. Schöberl and A. Wagner, "Methoden der Organischen Chemie" (Houben-Weyl), Vol. 9, E. Müller, Ed., 4th Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 72.

thiols, and aromatic 1,2-dithiols, as outlined in the following equation.

$$2RSO_2R + R'(SH)_2 \longrightarrow 2RSO_2H + RSSR'SSR$$

1 and 2 **3–10**

1, R = $Cl^-H_3N^+(CH_2)_2$
2, R = $AcNH(CH_2)_2$
3, R′ =  ; R = $AcNH(CH_2)_2$
4, R′ =  ; R = $AcNH(CH_2)_2$
5, R′ = $-(CH_2)_4-$; R = $Cl^-H_3N^+(CH_2)_2$
6, R′ = $-(CH_2)_4-$; R = $AcNH(CH_2)_2$
7, R′ = $-(CH_2)_2-$; R = $Cl^-H_3N^+(CH_2)_2$
8, R′ = $-(CH_2)_2-$; R = $AcNH(CH_2)_2$
9, R′ =  ; R = $Cl^-H_3N^+(CH_2)_2$
10, R′ =  ; R = $Cl^-H_3N^+(CH_2)_2$

Bisdisulfides represent, to the best of our knowledge, a class of compounds to which virtually no attention has been given, and the method of synthesis used appears to be a most convenient one. A further basis for interest in bisdisulfides is that 2-aminoethyl disulfide (cystamine) dihydrochloride is an effective antiradiation drug,[4] and it seemed that bisdisulfides containing 2-aminoethyl moieties also might show useful activity.

Reaction procedures were similar to those previously described,[2] as were isolation methods except for the aromatic bisdisulfide dihydrochlorides **9** and **10**. With **9** and **10**, the corresponding free bases apparently were too unstable to permit isolation in the usual way by rendering the reaction mixtures basic, extracting into solvents, and reconverting to salts; so the hydrochlorides were isolated by somewhat tedious crystallization procedures directly from the acidic reaction mixtures. The 1,1-bisdisulfide salts corresponding to the alicyclic 1,1-dithiols apparently were even less stable and could not be isolated at all, although the corresponding amides could be. Consistent with these observations, disproportionation experiments discussed later showed the N-acetyl 1,1-bisdisulfides **3** and **4** to be the least stable disulfides encountered in this series, followed closely by the aromatic *o*-bisdisulfide salts **9** and **10**.

Yields of the alicyclic 1,1 compounds **3** and **4** were 99 and 59%. Yields of the aliphatic 1,2- and 1,4-bisdisulfides **5–8** ranged from 76 to 93%, and of the aromatic salts **9** and **10** from 38 to 49%, because of the solubility properties, tedious isolation procedures, and low stability of **9** and **10**.

Disproportionation of unsymmetrical disulfides follows the equation, $2RSSR' \rightarrow RSSR + R'SSR'$. The study of thermal disproportionation in ordinary light was desirable to permit correlating structure and stability under usual laboratory conditions, as a matter of practical interest. Furthermore, if correlation of stability with protective activity were possible it should permit design of more effective antiradiation drugs. For our bisdisulfides, one product would be expected to be polymeric, cyclic, or unstable. Examples of all three types were found.

Disproportionations were effected by heating the disulfides in water, ethanol, or mixtures of the two (depending on solubility) for 25 min. to 72 hr. (depending on stability). The extent of disproportionation was difficult to estimate but could be obtained reasonably well by separating starting material and products in various ways. Thus disproportionation of the *gem*-bisdisulfide amides **3** and **4** produces acetylcystamine (water soluble), volatile products (hydrogen sulfide and a ketone), and elemental sulfur. The tetramethylene bis compounds, **5** and **6**, gave 1,2-dithiacyclohexane, readily separable by volatilization in steam or extraction. The aliphatic and aromatic 1,2-compounds **7–10** gave polymers, usually separable by filtration. Although the results are not highly accurate, they do suggest the relative ease of disproportionation. Details are summarized in Table I.

The *gem*-bisdisulfides **3** and **4** are the least stable aminoethyl mixed disulfides we have encountered. Both were completely destroyed in alcohol–water at 100° in 25 min. They gave acetylcystamine almost quantitatively and hydrogen sulfide, sulfur, and the corresponding ketone in yields indicating formation of 1 mole each per mole of starting material. The solution of the cyclohexyl compound **3** became turbid almost immediately at 100°, as did the cyclopentyl compound **4** after 4–5 min.; the cyclohexyl compound thus is the less stable. In alcohol, **3** disproportionated completely in 3 hr. at 100°, while **4** was recovered quantitatively (Table I). These results present two notable features. First, the effect of water is marked in the 1,1-bis compounds, and is not paralleled by at least one other bisdisulfide (**5**), which seems to be equally stable in alcohol and water. The change may result from a change in solvent properties, such as dielectric constant, or from change in the mode of disproportionation in alcohol to hydrolytic attack of water at the *gem*-disubstituted carbon atom. The products seem to be the same in either solvent; no evidence for separate existence of a dithiacyclopropane derivative was noted. Second, and more notable, is the marked difference in stability between **3** and **4** in alcohol. *This is a remarkable difference between identical side chains on a cyclohexane as opposed to a cyclopentane ring system.* It may well have valuable diagnostic applications and be worth considerable further study.

The tetramethylene bisdisulfides **5** and **6** both gave 1,2-dithiacyclohexane. Difficulty anticipated in obtaining this compound, in view of its reported properties,[5] did not materialize. The lack of polymerization encountered suggests that thermal disproportionation may be a good general method for preparation of 1,2-dithiacycloalkanes of suitable ring size.

Table I shows that the 1,4-alkylene bisdisulfides **5** and **6** are roughly comparable in stability with their 1,2-alkylene counterparts (**7** and **8**). The hydrochlorides **5** and **7** are rather less stable than the corresponding amides **6** and **8**, however, although these differences may result partly from necessary differences in the solvents used to effect homogeneous solutions. The bisaliphatic disulfides **5–8** were much more stable than the 1,2-phenylene or the 1,1-cycloalkylidene compounds but apparently less stable than the previously reported simple disulfide, 2-(*t*-butyldithio)ethylamine hydrochloride.[2]

(4) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, pp. 33, 34, 55, and 65.

(5) A. Schöberl and H. Gräfje, *Ann.*, **614**, 79 (1958).

TABLE I

DISPROPORTIONATION OF BISDISULFIDES

Disulfide	Solvent	Temp., °C	Time	% of 1 mole per mole of original disulfide: Starting material recovered	Acetylcystamine (A) or cystamine hydrochloride (B)	Dithiacyclohexane (C), polymer (D),[a] or H_2S (E)	Disproportionation, %[b]
3	95% EtOH	100	25 min.	~100	0 (A)	<1 (E)	0
3	95% EtOH	100	45 min.	37	50 (A)	22 (E)	50–63
3	95% EtOH	100	90 min.	10	78 (A)	46 (E)	78–90
3	95% EtOH	100	3 hr.	0	~100 (A)		~100
3	35% EtOH	100	25 min.	0	~100 (A)	73 (E)[c]	~100
4	95% EtOH	100	3 hr.	~100	0 (A)	0 (E)	0
4	35% EtOH	100	25 min.	0	~100 (A)	60 (E)[c]	~100
4	35% EtOH	100	100 min.	0	~100 (A)	75 (E)	~100
5 (free base)	35% EtOH	30	13 days	0		92 (C)	>92
5	35% EtOH	30	13 days	100	0 (B)	0 (C)	0
5	1 *M* HCl	30	13 days	100	0 (B)	0 (C)	0
5 (free base)	Water	100	25 min.	<10	60 (B)	>50 (C)	60–90
5	Water	100	25 min.			0 (C)	0
5	Water	100	3 hr.	57		17 (C)	17–43
5	95% EtOH	100	3 hr.	65		19 (C)	19–35
5	1 *M* HCl	100	3 hr.	<10		75 (C)	75–90
5	Water	100	22 hr.	30		57 (C)	57–70
5	Water	100	72 hr.			80 (C)	>80
6	Abs. EtOH	100	3 hr.	77			<23
6	Abs. EtOH	100	22 hr.	62			<38
6	Abs. EtOH	100	72 hr.			20 (C)	>20
7	Water	100	3 hr.	50		21 (D)	21–50
7	Water	100	22 hr.	28		43 (D)	43–72
8	Abs. EtOH	100	3 hr.	81		0 (D)	<19
8	Abs. EtOH	100	22 hr.	66		0 (D)	<34
9	Water	100	3 hr.	0		58 (91)[d] (D)	58–91
9	Water	100	22 hr.	0	96 (B)	95 (D)	95–96
10	Water	100	3 hr.	0		100[e] (D)	~100
10	Water	100	22 hr.	0	100 (B)	100 (D)	~100

[a] Values express the percent of 1 *M* proportion of monomeric repeating unit ($CH_3C_6H_3S_2$, $C_6H_4S_2$, or $C_2H_4S_2$) isolated as polymer from 1 *M* proportion of original disulfide. [b] Based on amounts of starting material recovered and products obtained, as recorded in columns 5–7. [c] In these experiments, cyclohexanone (40%) and cyclopentanone (35%) from **3** and **4**, respectively, were isolated as 2,4-dinitrophenylhydrazones by treatment of the cold-trap contents, after evaporation, with 2,4-dinitrophenylhydrazine. A gummy yellow solid residue of impure sulfur adhered to the sides of the ampoules; crude yield ~100% of 1 mole per mole starting material in each case; vacuum sublimation gave pure sulfur, m.p. 118–119°. [d] Figure in parentheses includes semipolymeric colloidal material which probably contained aminoethyl groups. [e] No polymer precipitated; 100 represents colloidal material separated by filtration through Celite.

Disproportionation of the salt **5** was the same in water as in alcohol, but was much greater when the salt was converted to the free base by reaction with 2 moles of alkali or when the salt **5** was heated in 1 *M* hydrochloric acid instead of water. Ultraviolet irradiation of an aqueous solution of **5** caused extensive disproportionation but gave no dithiacyclohexane.

The 1,2-bisalkylene and -arylene mixed disulfides **7**–**10** all gave polymers when heated in solution. The polymers seem to age on prolonged heating, and in most cases can then be separated from the mother liquor by filtration (through Celite) and so estimated. Cystamine hydrochloride was obtained as the second product after the complete disproportionation of the salts **9** and **10**. The arylene compounds **9** and **10** disproportionate rather readily, and are comparable with the analogous compound 2-(*p*-tolyldithio)ethylamine hydrochloride.[2] However, the free bases seem to be less stable, since **9** and **10** could not be isolated after rendering reaction mixtures containing them basic although this procedure was moderately satisfactory with the 2-(*p*-tolyldithio) compound.

Unavoidable experimental differences make comparison of stabilities of aminodisulfides difficult and uncertain. The results of Table I, taken in conjunction with previous work[2] and preparative experience, nevertheless suggest that when hot solutions are used in ambient light the trends of increasing stability will be about as follows: (a) free bases << hydrochlorides < amides; (b) 1,1-bisdisulfides (**3** and **4**, even though amides) < aromatic 1,2-bisdisulfide hydrochlorides (**9** and **10**) ≳ 2-(*p*-tolyldithio)ethylamine hydrochlorde[2] < 1,4- or 1,2-aliphatic bisdisulfide hydrochlorides (**5** and **7**) < 1,4- or 1,2-aliphatic bisdisulfide amides (**6** and **8**) ≳ 2-(*t*-butyldithio)ethylamine hydrochloride.[2] Efforts to develop theories which will link structure with stability toward disproportionation should be deferred until other correlations are available from work now in progress.

Experimental[6]

1,1-Bis(2-acetamidoethyldithio)cyclohexane (3).—1,1-Cyclohexanedithiol[7] (14.8 g., 0.1 mole) in methanol (100 ml.) was added to a stirred solution of 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**2**, 53.6 g., 0.2 mole)[2] in water (100 ml.)–methanol (200 ml.). After 2 hr., the solution was evaporated (25°) to a solid which was broken up with cold water (500 ml.) and isolated by filtration. Crystallization (aqueous acetone)

(6) Melting points are corrected unless otherwise specified. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Evaporation of solvents for isolation of products was effected under reduced pressure, usually with a rotary evaporator.

(7) J. Jentzsch, J. Fabian, and R. Mayer, *Chem. Ber.*, **95**, 1764 (1962).

gave 28.2 g. (74%) of **3** and evaporation of the mother liquor followed by crystallization from aqueous 2-propanol gave a further 9.8 g. (25%) of equally pure material, m.p. 108.5–109°, unaffected by further recrystallization. Aqueous 2-propanol is the preferred solvent.

Anal. Calcd. for $C_{14}H_{26}N_2O_2S_4$: C, 43.94; H, 6.85; N, 7.32; S, 33.52. Found: C, 43.96; H, 6.78; N, 7.23; S, 33.32.

1,1-Bis-2-(acetamidoethyldithio)cyclopentane (4).—The disulfide **4** preparation was exactly as for the cyclohexyl compound from cyclopentanedithiol[7] (4.08 g., 0.03 mole) and the thiolsulfonate **2** (16.08 g., 0.06 mole). The crude product (9.6 g., 87%, m.p. 102–103°) recrystallized from acetone gave pure **4** (6.5 g., 59%), m.p. 108–108.5°.

Anal. Calcd. for $C_{13}H_{24}N_2O_2S_4$: C, 42.36; H, 6.58; N, 7.60; S, 34.80. Found: C, 42.50; H, 6.35; N, 7.40; S, 34.96.

1,4-Bis(2-aminoethyldithio)butane Dihydrochloride (5).—1,4-Butanedithiol (15.25 g., 0.125 mole) in 35 ml. of alcohol was added to the thiolsulfonate **1** (64.25 g., 0.250 mole)[2] in 72 ml. of water with stirring. Stirring was continued for 2 hr., 50 ml. of alcohol being added to improve stirring. The solution was chilled, and the crude product collected, washed twice with absolute alcohol, and dried under vacuum, giving, 36.5 g. (fraction I), m.p. 187° dec. (Kofler). After filtration, 1.1 g. of taurine precipitated from the mother liquor. The mother liquor was evaporated to dryness, the residue taken up with water, and unchanged thiol removed by extraction with ether. The solution then was made alkaline with potassium hydroxide (16 g.) in ice–water in the presence of cold chloroform. Three chloroform extractions were made as quickly as possible. The combined chloroform extracts, after one washing with water, were immediately extracted with 10–12 ml. of 12 *N* hydrochloric acid diluted with water. Evaporation of the acid solution gave 3.5 g. (fraction II) of crystalline product, m.p. 192° dec. Fractions I and II were united and recrystallized from 2.6 l. of 85% acetone–15% water; undissolved taurine (melting point and infrared spectrum) was separated, amounting to 3.1 g. After 24 hr. at 5°, 25.9 g. of disulfide **5** with m.p. 198° dec. was collected. The mother liquor after concentration to 300 ml. and treatment as above (addition of base, extraction, etc.) yielded another crop (6.9 g.) of pure disulfide **5**, m.p. 198° dec. The total yield of recrystallized **5** was 32.8 g. (76%), and **5** was slightly hygroscopic; further recrystallization from aqueous acetone (as above) gave **5** with constant m.p. 197.5–198° dec.

Anal. Calcd. for $C_8H_{22}Cl_2N_2S_4$: C, 27.82; H, 6.42; N, 8.11; S, 37.12. Found: C, 28.00; H, 6.33; N, 7.99; S, 36.92.

1,4-Bis(2-acetamidoethyldithio)butane (6).—1,4-Dimercaptobutane (1.22 g., 0.01 mole) in 3 ml. of alcohol was poured into a solution of thiolsulfonate **2** (5.36 g., 0.02 mole) in 6 ml. of water with vigorous stirring. Two milliliters of alcohol was added to clarify the reaction mixture. Several minutes after the addition of thiol, a precipitate of disulfide **6** separated which was collected by filtration after 2 hr. of continued stirring (2.6 g.). Cooling and standing overnight resulted in a second crop of 0.9 g. The mother liquor on evaporation to thick sirup and addition of 10–15 ml. of water afforded a third crop of 100 mg. The three crops, containing acetyltaurine, were combined and recrystallized from ethyl acetate to constant melting point. There was obtained 2.70 g. (76%) of pure disulfide **6**, m.p. 83–84°.

Anal. Calcd. for $C_{12}H_{24}N_2O_2S_4$: C, 40.42; H, 6.78; N, 7.86. Found: C, 40.67; H, 6.81; N, 7.74.

1,2-Bis(2-aminoethyldithio)ethane Dihydrochloride (7).—1,2-Ethanedithiol (2.35 g., 0.025 mole) in 7 ml. of alcohol was added to the thiolsulfonate **1** (12.85 g., 0.05 mole) in 15 ml. of water with stirring. A precipitate soon separated; stirring, which was continued for 4 hr., was improved by addition of 5 ml. of alcohol. The precipitate (7.3 g.) was collected and washed with alcohol. Treatment of the mother liquor in the manner used for **5** gave only 0.1 g. more of crude disulfide **7**; the total yield of **7** was 7.4 g. (93%), m.p. 188–190°. After recrystallization to constant melting point from acetone–water (7:3), then from 95% alcohol, the melting point was 203–204° dec. During the recrystallization from alcohol, about one-tenth of the material each time was left behind (taurine).

Anal. Calcd. for $C_6H_{18}Cl_2N_2S_4$: C, 22.70; H, 5.72; N, 8.83; S, 40.41. Found: C, 22.34; H, 5.62; N, 9.16; S, 40.12.

3,4-Bis(2-aminoethyldithio)toluene Dihydrochloride (9).—The attempted synthesis of disulfide **9** by the procedure used for preparing 2-(*p*-tolyldithio)ethylamine hydrochloride[2] was unsuccessful because the free base disproportionated completely during chloroform extraction to give gummy polymer, even when the extraction was completed in seconds. The only pure product isolated was cystamine dihydrochloride. The purification procedure therefore was modified.

Toluene-3,4-dithiol (5 g., 0.032 mole) in 65 ml. of alcohol was added to the thiosulfonate **1** (16.5 g., 0.064 mole) in 38 ml. of water with stirring. The reaction flask was screened from light and stirring was continued for 4 hr. Taurine which precipitated (5 g.) was removed by filtration, and the turbid solution was clarified by filtration through Celite and Darco. The resulting clear solution on standing in normal laboratory light became turbid again in about half an hour. Water was completely evaporated and the waxy residue was rubbed several times with absolute alcohol to remove hypotaurine. Insoluble solid was dissolved in about 20 ml. of water. The resulting solution was filtered through Celite–Darco and after evaporation to 5 ml. and storage at 5° for 15 hr. yielded 65 mg. of taurine. Addition of absolute ethanol (50 ml.) caused crystallization of more taurine (580 mg.) which was separated after chilling for a few hours. The filtered solution on further addition of alcohol and chilling did not yield further precipitate. Upon complete evaporation of the solvent, there was obtained crystalline **9** having m.p. 170–172° dec., yield 1.6 g. (13%). The material was not recrystallized because of the likelihood of disproportionation.

Anal. Calcd. for $C_{11}H_{20}Cl_2N_2S_4$: C, 34.82; H, 5.31; N, 7.38; S, 33.80. Found: C, 34.80; H, 5.42; N, 7.26; S, 33.57.

Preparation on a larger scale (from 10 g. of dithiol) by essentially the same procedure afforded disulfide **9** in 38% yield, m.p. 174–174.5° dec.

1,2-Bis(2-aminoethyldithio)benzene Dihydrochloride (10).—A solution of 3.55 g. (25.0 mmoles) of 1,2-dimercaptobenzene[8] in 45 ml. of alcohol was added with stirring to a solution of 12.8 g. (50 mmoles) of thiolsulfonate **1** in 27 ml. of water. A few chips of Dry Ice were added in order to remove air from the reaction vessel. After addition was complete, cooling with ice–water for 5 min. resulted in a bulky precipitate. Stirring was continued after addition of 10 ml. of alcohol and removal of the ice bath. After 3 hr., the reaction mixture was chilled again and 4.80 g. of crystalline material was collected by filtration, m.p. 173–175° (Kofler) (fraction I). This proved to be disulfide **10** contaminated with about 15% of taurine (amount estimated from elemental analysis). After two recrystallizations from 95% ethanol, with removal of the nearly insoluble taurine, 3.70 g. (41%) of crystalline disulfide **10** was obtained having m.p. 189–190° dec.

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2S_4$: C, 32.87; H, 4.96; N, 7.67. Found: C, 32.79; H, 4.85; N, 7.74.

The mother liquor of fraction I after filtration was quickly evaporated to dryness, and the waxy residue thoroughly dried over phosphorus pentoxide. The resulting hard solid was triturated with five 40-ml. portions of absolute ethanol. Insoluble material was dissolved in 10 ml. of water; the solution was clarified by filtration through Celite, then concentrated to 5 ml., and chilled. After 3 hr., there was collected 661 mg. of a mixture of disulfide and unchanged thiosulfonate **1** (fraction II). By addition of 30 ml. of absolute ethanol to the mother liquor and chilling, 613 mg. of a mixture was obtained of disulfide, taurine, and thiolsulfonate **1** (fraction III). The mother liquor after addition of 30 ml. more of absolute ethanol and standing overnight at 5° yielded 159 mg. of disulfide **10** plus thiolsulfonate **1** (fraction IV). A similar mixture (899 mg., fraction V, was obtained by complete evaporation of solvent. Fractions II and V were combined and recrystallized from 100 ml. of hot ethanol. Taurine (190 mg.) was left undissolved. Thiolsulfonate **1** (448 mg.) precipitated overnight at 5°. Upon concentration of the solution to 20 ml., 405 mg. of pure **10** was obtained, m.p. 189–190° dec., and 368 mg. more, m.p. 178–180° dec., on cooling at 5°. These two crops showed identical infrared spectra; the total yield of disulfide was 4.47 g. (49%).

1,2-Dithiacyclohexane by Disproportionation of 5 and 6.—Disulfide **5** (3.45 g., 0.010 mole) was suspended in 15 ml. of water and heated in a round-bottomed flask at reflux temperature; the disulfide dissolved completely in the hot solution. After 4 hr. of heating, crystalline 1,2-dithiacyclohexane commenced to collect at the bottom of the ice–water cooled condenser. Heating

(8) A. Ferretti, *Org. Syn.*, **42**, 54 (1962).

was prolonged for 72 hr. but was discontinued for a few minutes every 4–8 hr. to permit removal of the cyclic disulfide. After 72-hr. heating, the amount of steam-distilled product that could still be collected was of the order of a few milligrams after several hours. The total amount of cyclic disulfide obtained was 963 mg. (80%) after drying. The product after sublimation (bath temperature 40° at 16–20 mm.) had m.p. 31–31.5°, lit.[5] m.p. 30.8–31.5°.

Anal. Calcd. for $C_4H_8S_2$: C, 39.96; H, 6.70; S, 53.34. Found: C, 39.84; H, 6.53; S, 53.24.

1,2-Dithiacyclohexane from disulfide **6** was obtained by the same procedure except that the system was heterogeneous throughout.

Disproportionation Procedures.—Solutions of 1 mmole of disulfide in 10 ml. of solvent were sealed in ampoules, dropped into a boiling water bath for the selected time, and then cooled as rapidly as possible in ice. Experiments in which 1,2-dithiacyclohexane was isolated by steam volatilization were carried out in flasks connected to condensers cooled with ice. Compounds formed or left unchanged routinely were characterized by melting point and mixture melting point and/or by the infrared spectrum.

Special modifications were the following.

A. 1,1-Biscycloalkylidene Disulfides 3 and 4.—After the heating period, ampoules were throughly cooled in Dry Ice, opened, quickly connected to an apparatus such that hydrogen sulfide could be flushed out with a slow stream of nitrogen into buffered (acetate) lead nitrate solution, and then allowed to warm to room temperature. Lead sulfide was collected and weighed. Ampoule contents were washed out and evaporated, solvent and volatiles being collected in a Dry Ice trap. Ketones were isolated from the trap contents as 2,4-dinitrophenylhydrazones. Acetylcystamine was extracted from the evaporation residues with ice cold water and was recrystallized from chloroform–ether. Unchanged starting materials were extracted with 2:3 alcohol–water mixture and crystallized by chilling. Sulfur was detected in the residues by insolubility in solvents other than carbon disulfide and was separated by vacuum sublimation.

B. Tetramethylene Bisdisulfides 5 and 6.—1,2-Dithiacyclohexane crystallized readily on ice cooling of the ampoules. It was isolated by filtration using a chilled funnel or better, with the salt **5**, by extraction into methylene chloride; despite the volatility of the dithiacyclohexane, it could be recovered and weighed reasonably satisfactorily by careful rapid evaporation of the dried extract. Evaporation of the aqueous layer or filtrate and consistency of the weight loss were used in several instances to substantiate the weight of dithiacyclohexane and thus provide assurance that only negligible amounts had escaped isolation. Water-soluble acetylcystamine was readily separated from insoluble **6**. Cystamine hydrochloride is readily soluble in ice-cold 2 *M* hydrochloric acid, but unchanged **5** is very slightly soluble, though soluble in water, thus permitting easy separation of these residues.

C. 1,2-Bisalkylene and -arylene Disulfides 7, 8, 9, and 10.—Disulfide **8** was reported previously.[2] Polymers which separated were removed by filtration using preweighed Celite and were estimated by drying to constant weight. Soluble products and unchanged starting materials were separated by solubility relationships obviously similar to those previously described and were recrystallized to purity.

Disproportionation of Disulfide 9 at Room Temperature.—The following experiment provides information on the speed at which disproportionation of this disulfide proceeds at room temperature in ordinary laboratory light. The disulfide **9** (379 mg.) was dissolved in 8 ml. of water and the solution was left to stand. Colloidal material separated slowly, and was removed repeatedly by filtration using preweighed Celite, which then was weighed after drying to constant weight. The total cumulative amount of colloidal polymer removed (in milligrams), and its per cent of total polymer theoretically possible were the following (after the number of days shown in parentheses): 59, 38 (7); 89, 58 (14); 119, 77 (21); 139, 90 (28), 152, 99 (37); 160, 104 (45).

Disproportionation of the Free Base of Disulfide 5 at Room Temperature.—Three portions, each 0.1725 g. (0.5 mmole), of **5** were dissolved in (a) 4 ml. of water plus 1.0 ml. of 1 *M* aqueous sodium hydroxide, (b) 5 ml. of water, and (c) 5 ml. of 1 *M* hydrochloric acid. An oil rapidly separated from (a). After 13 days (a) was acidified with 2 ml. of 1 *M* hydrochloric acid; (b) and (c) were clear but (a) contained an oil which crystallized on ice cooling. All three were extracted with methylene chloride; the extracts were dried ($MgSO_4$) and evaporated. (b) and (c) gave no residue but (a) gave 55 mg. (theoretical 60 mg.). Residues on evaporation of the aqueous layers were (b) 0.173 g., (c) 0.171 g., and (a) 0.168 g.; the former two corresponded to no disproportionation and the last (allowing for 58.5 mg. of sodium chloride) to complete disproportionation.

The Preparation of Heterocyclic Organophosphorus Compounds by Cyclodehydrohalogenation[1]

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5-Chlorodibenzophosphole and 10-chlorophenoxaphosphine have been prepared in 6 and 24% yields, respectively, by dehydrohalogenation of 2-biphenylyl- and 2-phenoxyphenylphosphonous dichlorides. The phosphonous dichlorides were not isolated but underwent cyclization during the manipulations incident to their attempted isolation. 2-Benzylphenylphosphonous dichloride, however, could be isolated. It underwent cyclodehydrohalogenation to yield 5-chloro-5,10-dihydrodibenz[*b,e*]phosphorin when heated with anhydrous zinc chloride. The hydrolysis and oxidation of all three cyclic chlorophosphines yielded the corresponding cyclic phosphinic acids.

One method for preparing heterocyclic arsenic and antimony compounds is by cyclodehydration of appropriately substituted arylarsonic or arylstibonic acids. Thus phenazarsinic acid (I)[2] is readily prepared by heating *o*-arsonodiphenylamine with hydrochloric acid.[3] Freedman and Doak, however, have found that both 2-biphenylylphosphonic acid and 2-phenoxyphenylphosphonic acid fail to undergo cyclodehydration under a variety of experimental conditions.[4,5] Similarly, Campbell and Way have reported the failure of 2-biphenylylphenylphosphinic acid to cyclize when heated with polyphosphoric or sulfuric acids.[6] They were successful, however, in cyclizing the acid by heating with phosphorus pentachloride and nitrobenzene. In

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(2) In our previous papers on heterocyclic phosphorus compounds, we have employed the nomenclature of F. G. Mann, "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth, and Silicon," Interscience Publishers, Inc., New York, N. Y., 1950. At the suggestion of a referee and of the editor we have used Ring Index nomenclature in the present paper.

(3) C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 2499 (1927).

(4) This compound has previously been named phosphafluorinic acid; *cf.* L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **21**, 238 (1956).

(5) L. D. Freedman, G. O. Doak, and J. R. Edmisten, *ibid.*, **26**, 284 (1961).

(6) I. G. M. Campbell and J. K. Way, *J. Chem. Soc.*, 2133 (1961).