

Antiradiation Compounds VIII.

Reaction of Thiols with Cyanogen Bromide

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The reaction of a thiol with cyanogen bromide provides a specific synthesis of disulfides without further oxidation. The reaction is apparently general, and was successful for MEA, MEG, and aliphatic, aromatic, and amino thiols. Oxidation of MEA with 3 per cent hydrogen peroxide also gave the disulfide, but similar oxidation of MEG gave the thiolsulfinate, distinguishable from the disulfide by infrared absorption in the 1100 cm^{-1} region.

THE REACTION of dithiols with cyanogen chloride has been found to result in the formation of cyclic imino dithioester hydrochlorides (1). With the assumption that 2-mercaptoethylamine hydrochloride (MEA) might react with cyanogen bromide in analogous fashion, either an imino dithioester hydrochloride or iminothiazolidine would be obtained, and provide possibly an active antiradiation agent. The former may be expected to liberate MEA *in vivo*, and in the latter case, some thiazolidines are known to be radioprotective (2). A stable, white, granular product was obtained from the proposed reaction (2 moles of MEA hydrochloride with 1 mole of cyanogen bromide) which did not reduce iodine and gave a positive test for the disulfide linkage with Grote's reagent (3). The melting point ($221\text{--}222^\circ$) was somewhat higher than those recorded for the disulfide of MEA hydrochloride (203° , 210° , 212° , 216°) (4), however, and the carbon-hydrogen analysis was somewhat low for this compound.

A pure sample of the disulfide of MEA hydrochloride was accordingly required for comparison. By iodine oxidation of MEA hydrochloride, a product was obtained for which the melting point (217°) agreed with that reported by Schoberl (5). By use of alkaline peroxide (3%), a product was obtained which melted at $222\text{--}224^\circ$ and gave the correct analytical data for the disulfide. The ultraviolet, infrared,¹ and Raman² spectra of the disulfide and the product of cyanogen bromide oxidation proved to be identical. (See Fig. 1 for infrared spectrum.) The Raman spectra showed strong absorption at 515 and 650 cm^{-1} , expected for S-S and C-S stretching (6). It was suspected that the low C-H assay values might be due to the presence of bromide ion, but a correct analysis for chlorine was obtained, and no bromide ion was detected by the chlorine water-carbon tetrachloride test. In addition, a dibenzoyl derivative was obtained that was identical in yield and properties to that prepared from the disulfide.

The reaction of cyanogen bromide with other thiols was observed, and in each case the disulfide was formed. With 2-mercaptoethylguanidine (MEG), a compound corresponding to the disulfide (7) was obtained from cyanogen bromide oxidation, and a compound whose analytical data and infrared absorption spectra indicated the thiolsulfinate was ob-

tained from oxidation by 3% hydrogen peroxide at 40° . A strong peak at 1115 cm^{-1} (Fig. 2), absent in the disulfide (Fig. 3), provided spectral evidence for the thiolsulfinate (8). This region of the spectrum (Fig. 2) was identical when observed in either Nujol or KBr.

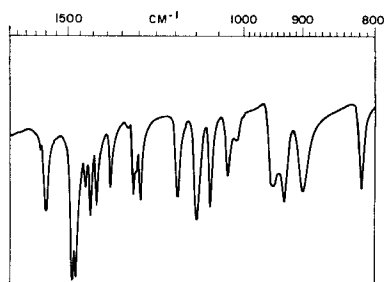


Fig. 1.—I.R. spectrum of 2-aminoethyl disulfide dihydrochloride in KBr.

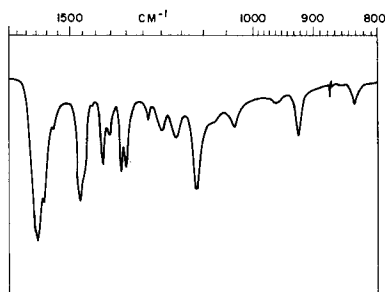


Fig. 2.—I.R. spectrum of 2-guanidinoethyl 2-guanidinoethanethiolsulfinate dihydrobromide in Nujol.

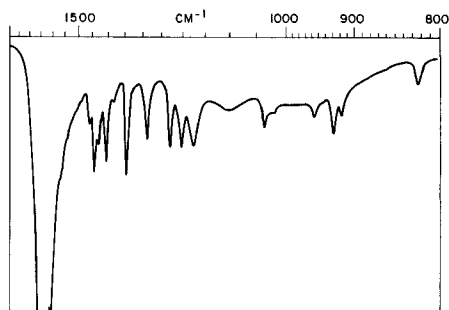


Fig. 3.—I.R. spectrum of 2-guanidinoethyl disulfide dihydrobromide in KBr.

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¹ Supplied by Dr. Winthrop E. Lange.

² Done through the courtesy of Professor R. C. Lord, Massachusetts Institute of Technology.

Other thiols subjected to cyanogen bromide oxidation included cysteine, homocysteine, 2-diethylaminoethanethiol hydrochloride,³ 1-amino-2-propanethiol hydrochloride,⁴ thiophenol, heptanethiol, dodecanethiol, *o*- and *p*-aminobenzenethiol hydrochloride, and *o*-, *p*-, and α -toluenethiol. The formation of a disulfide in each case was shown by melting point (except for two cases, the disulfides are known), elemental analysis, and infrared absorption spectra (two or three peaks at 1050–1250 cm^{-1} which were fairly strong in the case of the aromatic and amino-alkyl disulfides). These peaks are apparently due to CH_2 or aryl CH wag of CH_2 or CH adjacent to sulfur (6). Bredereck *et al.* (8) have shown two peaks near 1100 cm^{-1} for an aryl disulfide.

Antiradiation testing of MEA disulfide dihydrochloride at the Walter Reed Army Institute of Research, through the courtesy of Drs. D. P. Jacobus and T. R. Sweeney, showed the compound to possess good protective properties in mice *versus* 825 r., a finding which is in agreement with previous reports (9).

EXPERIMENTAL

Analyses for carbon, hydrogen, and nitrogen were done by Weiler and Strauss, Oxford, England, or by Carol K. Fitz, Needham, Mass. Sulfur and chloride analyses were done by Parr bomb peroxide fusion. Melting points were taken on a Mel-Temp apparatus and are corrected. Infrared absorption spectra were obtained with a Perkin-Elmer model 137B spectrometer.

2-Aminoethyl Disulfide Dihydrochloride.—By Cyanogen Bromide Oxidation.—Cyanogen bromide (3.63 Gm., 0.034 mole) (Eastman Organic Chemicals) was added to a solution of 2-aminoethanethiol hydrochloride (7.78 Gm., 0.068 mole) (Aldrich Chemical Co.) in 20 ml. of absolute ethanol. A precipitate formed immediately, with liberation of heat, and was filtered, washed with ethanol, and air dried. A second crop was obtained by addition of ether to the filtrate. After recrystallization from 95% ethanol, a yield of 3.0 Gm. (78%) was obtained; m.p. 221–222°. [Lit. m.p. 216° (5)] λ_{max} . 245 μ .

Anal.—Calcd. for $\text{C}_4\text{H}_{14}\text{Cl}_2\text{N}_2\text{S}_2$: C, 21.33; H, 6.27; Cl, 31.49; N, 12.43. Found: C, 19.87; H, 5.93; Cl, 31.30; N, 12.25.

Benzoylation in pyridine with exactly 2 moles of benzoyl chloride for 4 days at 25° gave a 71% yield of the dibenzoyl derivative, m.p. 132–133°. [Lit. m.p. 132° (10).]

By Alkaline Peroxide Oxidation.—A solution of 5.7 Gm. (0.5 mole) of 2-aminoethanethiol hydrochloride in 10 ml. of water was neutralized with a solution of 2.1 Gm. (0.05 mole) of lithium hydroxide in 20 ml. of water. The solution was cooled in an ice bath, and 3% hydrogen peroxide solution was added dropwise with stirring until the reaction solution gave a negative test for thiol with nitroprusside solution. The resulting solution was acidified with hydrochloric acid (1:1) solution to a pH of 2, concentrated to one-half its volume, and cooled. A semisolid resulted

which was triturated in a mortar with 97.5% ethanol, washed with absolute ethanol, and dried *in vacuo*, giving 3.4 Gm. (60%) of crystalline product, m.p. 222–224°.

Anal.—Calcd. for $\text{C}_4\text{H}_{14}\text{Cl}_2\text{N}_2\text{S}_2$: C, 21.33; H, 6.27; Cl, 31.49; N, 12.43; S, 28.48. Found: C, 21.56; H, 6.32; Cl, 31.99; N, 12.21; S, 28.41.

The dibenzoyl derivative was prepared as above in 72% yield, m.p. 134–135°.

2-Guanidinoethyl Disulfide Dihydrobromide.—*S*-(2-Aminoethyl) isothiuronium bromide hydrobromide (11.2 Gm., 0.04 mole) (Matheson, Coleman and Bell) was dissolved in 30 ml. of water and 6 ml. of concentrated ammonium hydroxide and treated with cyanogen bromide (2.12 Gm., 0.02 mole) with stirring. After 2 hr., the orange solution was refrigerated, and a cream colored solid was isolated and recrystallized from ethanol. The yield was 1.8 Gm. (23%), m.p. 195–196°. [Lit. m.p. 195–197° (7).]

Anal.—Calcd. for $\text{C}_6\text{H}_{18}\text{Br}_2\text{N}_6\text{S}_2$: C, 18.1; H, 4.5; N, 21.1; S, 16.1. Found: C, 17.6; H, 4.5; N, 20.5; S, 16.0.

2-Guanidinoethyl 2-Guanidinoethanethiolsulfinate Dihydrobromide.—*S*-(2-Aminoethyl)isothiuronium bromide hydrobromide (14.0 Gm., 0.05 mole) was dissolved in 12.5 ml. of concentrated ammonium hydroxide, and 100 ml. of 3% hydrogen peroxide was added in 4 portions with stirring over a 2-hr. period. The solution was kept at 40° during the addition. It solidified on cooling, and the solid was triturated with absolute ethanol and recrystallized from ethanol. The yield was 3.5 Gm. (33%) of white crystalline solid, m.p. 175–176°.

Anal.—Calcd. for $\text{C}_8\text{H}_{18}\text{Br}_2\text{N}_6\text{OS}_2$: C, 17.4; H, 4.4; N, 20.3; S, 15.5. Found: C, 17.2; H, 4.2; N, 20.1; S, 15.4.

Other Thiols.—2-Diethylaminoethyl disulfide was obtained as the dihydrobromide, m.p. 233–235°, apparently by using an excess of cyanogen bromide.

Anal.—Calcd. for $\text{C}_{12}\text{H}_{30}\text{Br}_2\text{N}_2\text{S}_2$: C, 33.80; H, 7.11; N, 6.57; S, 15.05. Found: C, 34.81; H, 7.12; N, 6.53; S, 15.55.

o-Aminophenyl disulfide was obtained as the dihydrochloride, m.p. 225–227°, not previously reported.

Anal.—Calcd. for $\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{N}_2\text{S}_2$: C, 44.89; H, 4.36; N, 8.72; S, 19.96. Found: C, 44.75; H, 4.71; N, 8.34; S, 19.40.

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⁴ Supplied by T. R. Sweeney, Walter Reed Army Institute of Research.