Acknowledgment.—The authors wish to thank the Petroleum Research Fund (Grant No. 726) for partial support of this work.

Reactions of 1-Chloro-2,3-epithiopropane

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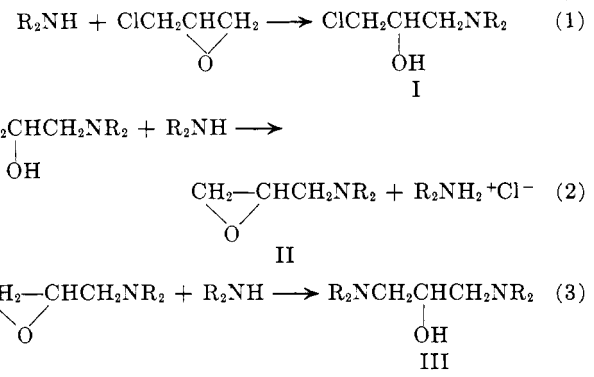
Received November 26, 1963

There have been numerous investigations reported on the reaction of epichlorohydrin with amines, of which the references listed[1,2] are representative. In these reactions, with either primary or secondary amines, it has been established that the following sequence can occur, with the final product dependent mainly on the relative molar amount of amine used.



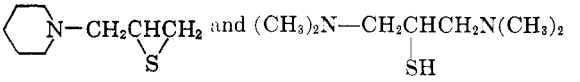
In work at this laboratory, reactions of amines with the sulfur analog of epichlorohydrin, 1-chloro-2,3-epithiopropane, have been investigated. In *no* case, regardless of the molar ratio of reactants, the manner of addition, the solvent, or the conditions of the reaction, have sulfur analog compounds corresponding to I, 1-N-substituted amino-3-chloro-2-propanethiols, been isolated.

With secondary amines, sulfur analog products corresponding to II, 1-N-disubstituted amino-2,3-epithiopropanes, and to III, 1,3-bis(N-disubstituted amino)-2-propanethiols, were formed in relative amounts dependent chiefly on the amount of amine used. Tables I and II list the physical constants, analytical data, and some derivatives for the compounds prepared. Although the course of the reactions has not been definitely established, it is believed that the same sequence occurs as in the case of epichlorohydrin, with step 2 proceeding at a much faster rate than step 1. Direct nucleophilic displacement of chlorine by amine to give products of type II in one step does not seem likely in view of the usual lower relative speed, under the conditions used, of this type of reaction as compared to the opening of the sulfide ring, nor in view of the usual close analogy of reactions of oxiirane and thiirane rings with nucleophilic reagents. Using a reactant mole ratio of 1:1, especially if the amine was added to the sulfide, with both in ether or petroleum ether (b.p. 30–60°) solution, gave predominantly the amino sulfides as products in yields varying from fair to moderately good based on the available amine. With dimethylamine, however, polymerization of the amino sulfide occurred very easily during distillation and on standing at room temperature, so that the product could not be directly analyzed. When methanol was used as solvent with dimethylamine or diethylamine, only polymers were obtained. With the three heterocyclic amines tried, methanol could be used as solvent and the amino sulfides could be isolated, but in lower yield than when ether was used as solvent, due to some polymerization. The amino sulfides, once isolated, reacted very readily with additional amine (except in the case of di-*n*-butylamine as noted subsequently) to form the 1,3-bis(N-disubstituted amino)-2-propanethiols.

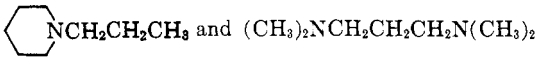
With a reactant ratio of 2 or more moles of amine to 1 of sulfide, both types of products were generally obtained. Apparently steric hindrance plays a role in determining the ratio of these products, since, for example, in the case of di-*n*-butylamine none of the 1,3-bis(dibutylamino)-2-propanethiol was ever formed regardless of the amount of amine used or conditions of the reaction.

In order to demonstrate the direction of ring opening in both steps 1 and 3, desulfurization by commercial Raney nickel catalyst of one of the amino sulfides and one of the diaminopropanethiols was employed.

The following structures were shown to be correct,

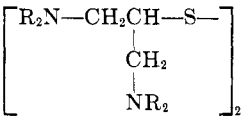


since, on treatment of each individually with Raney nickel in ethanol, these compounds were obtained.



Thus both 1-chloro-2,3-epithiopropane and the 1-N-disubstituted amino-2,3-epithiopropanes open in the so-called "normal" manner by cleavage at the primary carbon–sulfur bond when treated with amines.

In some cases the 1,3-bis(N-disubstituted amino)-2-propanethiols were oxidized with alcoholic iodine to the following corresponding disulfides.



These were either isolated and purified directly as the dihydroiodide salts or the free tetraaminodisulfide was isolated and then converted to the tetrahydrochloride salt.

In the reaction of primary amines with 1-chloro-2,3-epithiopropane, no simple compounds could be isolated and amino sulfide polymers appeared to be the only products. This was not unexpected, since the amino sulfide monomer contains a secondary amine group which can react readily with the sulfide ring in another molecule, thus leading to polymers of the following type.

(1) H. Gilman, *et al.*, *J. Am. Chem. Soc.*, **68**, 1291 (1946).
(2) D. L. Heywood and B. Phillips, *ibid.*, **80**, 1257 (1958).

TABLE I

1-N-DISUBSTITUTED AMINO-2,3-EPITHIOPROPANES

$R_2NCH_2CHCH_2$ (S bridge)

Amine group	B.p., °C. (mm.)	$n^{25}D$	Anal., % C Calcd.	C Found	H Calcd.	H Found	Derivatives (m.p., °C.)
Dimethylamino[a]	51–53 (12)						Hydrochloride (160–161) Calcd.: C, 39.08. Found: C, 39.04 Calcd.: H, 7.87. Found: H, 7.82 Picrate (140–141.5)
Diethylamino	62–63 (2.5)[b] 45–46 (0.7)	1.4854[b]	57.88	57.71	10.41	10.36	Hydrochloride (153–154 dec.)
Di-*n*-butylamino	81–82 (0.2)	1.4760	65.55	65.79	11.51	11.74	
Piperidino	66 (0.3)	1.5173	61.08	60.77	9.61	9.56	Hydrochloride (183–184 dec.) Calcd.: C, 49.59. Found: C, 49.68 Calcd.: H, 8.33. Found: H, 8.45 Bromine addition product dihydrochloride (209–210)
Morpholino	78–79 (0.2)	1.5211	52.80	53.01	8.23	8.39	Hydrochloride (193.5–194)
Pyrrolidino	55 (0.3)	1.5165	58.69	58.54	9.15	8.95	Picrate (98–99.5)

[a] The product from dimethylamine polymerized readily and good physical constants and analytical data could not be obtained. [b] R. D. Schuetz and R. L. Jacobs [*J. Org. Chem.*, **26**, 3467 (1961)] reported b.p. 75° (11 mm.), $n^{25}D$ 1.4832, and E. P. Adams, *et al.*, [*J. Chem. Soc.*, 2649 (1960)] reported b.p. 72° (14 mm.), $n^{20}D$ 1.4857, as prepared from the epoxide.

TABLE II

1,3-BIS(N-DISUBSTITUTED AMINO)-2-PROPANETHIOLS

$R_2NCH_2CHCH_2NR_2$ (SH)

Amine group	B.p., °C. (mm.)	$n^{25}D$	Anal., % C Calcd.	C Found	H Calcd.	H Found	Derivatives (m.p., °C.
Dimethylamino	67–68 (3)	1.4696	51.48	51.37	11.11	11.30	
Diethylamino	92–94 (1)	1.4687	60.49	60.77	12.00	11.76	Disulfide dihydroiodide (iodine oxidation product) (164.5–165.5 dec.) Calcd.: C, 38.26. Found: C, 38.35 Calcd.: H, 7.59. Found: H, 7.62
Piperidino	123–124 (1)	1.5102	64.41	64.28	10.81	10.63	Disulfide tetrahydrochloride (202.5–203.5 dec.) Calcd.: Cl, 22.56. Found: Cl, 22.27
Morpholino	137–139 (0.3) m.p. 49.5–50.5 (ligroin)	1.5219	53.62	53.42	9.00	8.81	Hydrochloride (183)
Pyrrolidino	110–111 (0.3)	1.5116	61.63	61.39	10.35	10.26	

$$\left(-N(R)-CH_2-CH(SH)-CH_2-\right)_x$$

The reactions of 3-chloro-1,2-epithiopropane with chlorine and bromine in anhydrous solvents such as chloroform and with aqueous chlorine were carried out several years ago and follow the general course of such reactions reported earlier for other cyclic sulfides.[3–5] An equimolar amount of chlorine passed into a solution of 3-chloro-1,2-epithiopropane in chloroform apparently opens the ring in an "abnormal" manner to yield bis(2,3-dichloropropane) disulfide, $(ClCH_2CHCH_2S-)_2$ (Cl). Structure proof was based on the work of Davies and Savige,[6] who demonstrated that aqueous hydrochloric acid opened the ring of 3-chloro-1,2-epithiopropane at the secondary carbon–sulfur bond to give 2,3-dichloro-1-propanethiol. This preparation was repeated and the thiol was oxidized with iodine in alcohol solution to bis(2,3-dichloropropane) disulfide. This compound had the same melting point as the product of reaction of chlorine and 3-chloro-1,2-epithiopropane, and a mixture melting point determination showed no depression. It also is assumed then that the addition product with bromine is bis-(2-bromo-3-chloropropane) disulfide.

No structure proof was carried out for the reaction product of aqueous chlorine and 3-chloro-1,2-epithiopropane. It is assumed, however, that ring cleavage takes place at the secondary carbon–sulfur bond as with anhydrous chlorine to give the product 2,3-dichloro-1-propanesulfonyl chloride, $ClCH_2CHCH_2SO_2Cl$ (Cl).

Experimental[7]

1-Chloro-2,3-epithiopropane was prepared by the method of Culvenor, *et al.*,[8] in yields of 50–60%, b.p. 60–61° (45 mm.), $n^{25}D$ 1.5222 [lit.[8] b.p. 79–81° (114 mm.), $n^{20}D$ 1.5280].

Reactions of Secondary Amines with 1-Chloro-2,3-epithiopropane. A. In 1:1 Molar Ratio.—A solution of the amine in five times its volume of ether or petroleum ether (b.p. 30–60°) was added dropwise with stirring at room temperature (0° for dimethylamine) to a solution of 1-chloro-2,3-epithiopropane

(3) J. M. Stewart and H. P. Cordts, *J. Am. Chem. Soc.*, **74**, 5880 (1952).
(4) J. M. Stewart and C. H. Burnside, *ibid.*, **75**, 243 (1953).
(5) J. M. Stewart, *J. Org. Chem.*, **28**, 596 (1963).
(6) W. Davies and W. E. Savige, *J. Chem. Soc.*, 774 (1951).
(7) Melting points are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn.
(8) C. C. J. Culvenor, W. Davies, and K. H. Pausacker, *J. Chem. Soc.*, 1050 (1946).

in seven times its volume of the same solvent. After the addition was complete, the mixture was allowed to stand for a period of 18–24 hr. Longer reaction times increased the amount of polymer formed. The precipitated hydrochloride was removed by filtration, the solvent and unchanged starting materials were stripped under reduced pressure, and the products were separated by vacuum distillation. Under these conditions the following yields of 1-N-disubstituted amino-2,3-epithiopropane (based on 50% of the amine used) were obtained for the indicated amine: dimethylamine, 0% (polymers only); diethylamine, 30–40%; dibutylamine, 72%; piperidine, 60–65%; and morpholine, 62.5%. Methanol as solvent appeared to give much faster reactions but also increased the amount of polymer formation. In one experiment with piperidine and a reaction time of only 5 hr., however, a yield of 75% of 1-piperidino-2,3-epithiopropane was obtained when methanol was the solvent.

B. In a Ratio of 2 Moles of Amine to 1 Mole of 1-Chloro-2,3-epithiopropane.—The same procedure was followed as described in A. The two types of products were separated by distillation. Yields of 1-N-disubstituted amino-2,3-epithiopropanes (based on the 1-chloro-2,3-epithiopropane used) varied from 30–48%, and the yields of 1,3-bis(N-disubstituted amino)-2-propanethiols (based on 25% of the amount of *amine* used) varied from 25–45%. With di-*n*-butylamine, no thiol-type product was formed, and with diethylamine the thiol-type product was formed in small per cent. The reaction with pyrrolidine appeared to be unusually fast, and, in one run in which the amine was added all at once in petroleum ether solution and the reaction period was only 5 hr., yields of 48.4% of the amino sulfide-type product and 34% of the thiol were obtained.

C. In a Ratio of 3 Moles or More of Amine to 1 Mole of 1-Chloro-2,3-epithiopropane.—In these experiments the sulfide solution was added dropwise with stirring to the excess of amine, but otherwise the procedure was the same as described in A. With dimethylamine and diethylamine both types of products were obtained, with piperidine and morpholine only the thiol. Yields were as follows: for dimethylamine, 37% amino sulfide and 33% thiol; for diethylamine, 35% amino sulfide and 50% thiol; for piperidine, 60–65% thiol; and for morpholine, 54% thiol.

Infrared Spectral Data for 1-N-Disubstituted Amino-2,3-epithiopropanes.—Infrared spectra were determined on a Beckman IR-5 spectrophotometer. Absorption bands which were *common* to all of the examples of this type of compound prepared were as follows: $\lambda_{max}^{CCl_4}$ 3.4, 3.6, 6.9, 7.2–7.3, and 9.6 μ. For comparison, 1-chloro-2,3-epithiopropane showed characteristic absorption bands at 3.35, 6.92, 7.95, 8.64, 9.18, 9.6, 13.96, and 14.9 μ.

Raney Nickel Desulfurizations in Structure Proofs.—Desulfurizations were carried out in absolute ethanol using commercial Raney nickel (No. 28 Raney Active Nickel, Raney Catalyst Co., Chattanooga, Tenn.) in an amount equal to ten times the amount of compound, and the mixtures were allowed to stand for about an hour at room temperature with frequent shaking. Evolution of heat was noticed. From the amino sulfide containing a piperidino group was obtained an amine which was immediately converted to a picrate derivative and this, after three recrystallizations from absolute ethanol, melted at 105–107°. This agrees with the m.p. 108° reported by Magnusson and Schierz[9] for N-*n*-propylpiperidine, whereas N-isopropylpiperidine picrate was reported melting at 153°.

From the diaminothiol product containing dimethylamine groups was obtained an amine which also was converted at once to the picrate and this, after one recrystallization from water, melted at 207–208°, after darkening and deformation from 205–207°. This agrees with the m.p. 207° reported by Clarke[10] for the picrate of N,N,N′,N′-tetramethyl-1,3-propanediamine, whereas N,N,N′,N′-tetramethyl-1,2-propanediamine picrate is reported[11] to melt at 190°.

Reactions of 1-Chloro-2,3-epithiopropane and Anhydrous Solutions of Chlorine and Bromine.—The general procedure described for other cyclic sulfides[3-5] was employed. Reaction with chlorine gave a 37% yield of liquid product, b.p. 157–160° (1 mm.), which, after two further distillations, crystallized in the receiver. Recrystallization from 95% ethanol gave colorless crystals, m.p. 67–69°. A mixture melting point of this product and the disulfide obtained by iodine oxidation of 2,3-dichloro-1-propanethiol prepared from reaction of 1-chloro-2,3-epithiopropane and concentrated hydrochloric acid showed no depression. The compound then is bis(2,3-dichloropropane) disulfide.

Anal. Calcd. for $C_6H_{10}Cl_4S_2$: C, 25.01; H, 3.50. Found: C, 24.89; H, 3.51.

Reaction with bromine gave a quantitative yield of slightly red solid which was recrystallized from 95% ethanol to give colorless crystals, m.p. 80–82.5°, assumed to be bis(2-bromo-3-chloropropane) disulfide.

Anal. Calcd. for $C_6H_{10}Br_2Cl_2S_2$: C, 19.11; H, 2.67. Found: C, 19.39; H, 2.64.

Reaction of 1-Chloro-2,3-epithiopropane and Aqueous Chlorine.—This reaction was carried out as described for other cyclic sulfides.[3-5] After one distillation, a yield of 47% was obtained. Redistillation gave a colorless liquid, b.p. 82.5–83.5° (1 mm.), $n^{20}D$ 1.5137, assumed to be 2,3-dichloro-1-propanesulfonylchloride.

Anal. Calcd. for $C_3H_5Cl_3O_2S$: C, 17.04; H, 2.38. Found: C, 17.36; H, 2.35.

Acknowledgment.—This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of this fund.

(9) H. W. Magnusson and E. R. Schierz, *Wyoming Univ., Publ.*, **7**, 1 (1940).

(10) H. T. Clarke, *J. Chem. Soc.*, **103**, 1699 (1913).

(11) R. Paul and S. Tchelitcheff, *Compt. rend.*, **238**, 2089 (1954).

Optical Resolution of (±)-1-Amino-2-propanethiol[1]

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Received December 3, 1963

The recently reported finding that (−)-2-(2-aminobutyl)-2-thiopseudourea hydrobromide is twice as effective in protecting mice against a single dose of lethal X-irradiation as the (+)-isomer[2] suggests that important differences may be found between other enantiomeric pairs of radioprotective agents previously evaluated as racemic mixtures. The optical resolution of (±)-1-amino-2-propanethiol [(±)-I] was selected for investigation because this compound has been reported to afford good radioprotection.[3]

The resolution of (±)-I was first approached *via* the crystalline salts of (±)-2-(benzylthio)propylamine with (−)-malic acid and (+)-tartaric acid, which were to be subsequently debenzylated; but optical enrichment was not attained by repeated recrystallization of these salts. The resolution was then undertaken by a method recently applied by Taguchi, *et al.*,[4] to the resolution of (±)-*trans*-2-aminocyclohexanethiol *via* the thiazolidine formed with D-glucose. The reported resolution suggests a general method, but the paucity of experimental details necessitated development of each step when applied to the resolution of (±)-I. The process that eventually evolved is outlined below.

(1) This investigation was supported by the U. S. Army Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) D. G. Doherty and R. Shapira, *J. Org. Chem.*, **28**, 1339 (1963); see also Abstracts of Papers, International Congress of Radiation Research, Burlington, Vt., Aug. 10–16, 1958; *Radiation Res.*, **9**, 107 (1958).

(3) F. Yu. Rachinskii, A. S. Mozzhukhin, N. M. Slavachevskaya, and L. I. Tank, *Usp. Khim.*, **28**, 1488 (1959); J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p. 66.

(4) T. Taguchi, T. Takatori, and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), **10**, 245 (1962).