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SYNTHESIS OF SOME VICINAL DITHIOLS AND THEIR DERIVATIVES[1]

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The efficacy of BAL (British Anti-Lewisite, 2,3-dimercaptopropanol) in the treatment of arsenical burns and systemic arsenical poisoning has been described in several recent articles (1, 2, 3). Following ghe transmittal of details of the chemistry, preparation, and clinical study of BAL by the British, an intensive program of study was initiated in this country on related compounds with the objective of uncovering more effective and less toxic candidates for antidotal use. This paper deals with that part of the program which aimed specifically at the synthesis of dithiol therapeutic agents. The preparation of a number of dithiols and derived compounds prepared on this program has already been reported (4, 5, 6). These were submitted for pharmacological and physiological tests to several other laboratories working on programs sponsored by the National Defense Research Committee and the Committee on the Treatment of Gas Casualties.

Earlier work by other investigators had indicated that 1,2-dithiols were more efficacious in arsenical therapy than analogs in which the mercapto groups were not on adjacent carbon atoms, and consequently major effort was directed toward the synthesis of the vicinal derivatives. In those cases where a particular functional group imparted some desirable characteristic to the dithiol, as shown by biological tests, homologs of that candidate were prepared, so that structure and efficacy might be further correlated. In Table I are listed the dithiols synthesized along with their significant physical properties.

The classical methods for obtaining thiols failed in many cases to give the desired substituted dithiols and new modifications and methods had to be developed for some of the compounds obtained. Contributing to the difficulties encountered was the instability of 1,2-dithiols, particularly those containing other functional groups. The side reactions encountered were chiefly those involving the elimination of halogen acid or reduction of the dihalide by the thiolating agent.

Thiolations using sodium hydrosulfide under hydrogen sulfide pressure were successful in the preparation of 2,3-dimercaptopropylurethan, 2,3-dimercaptopropylurea, 3,4-dimercaptobutanol, and 2,3-dimercaptopropionaldehyde diethyl acetal from the corresponding dibromides; however, the method failed in most other cases. For example, when applied to the synthesis of dimercaptopropionic acid, dimercaptosuccinic ester, or 2,3-dimercaptobutanol, no dithiols were obtained, but only mixtures of low sulfur content. During attempted isolation

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of several of the BAL analogs which apparently reacted normally with the thiolating agent, loss of thiol titer was experienced through oxidation, dehydration, or dehydrosulfurization. Thus, dibromopropylacetamide reacted with sodium hydrosulfide in methanol at room temperature to give the corresponding dithiol; however, distillation under the mildest conditions resulted in dehydration to a cyclic thioamide believed to be 2-methyl-5-mercapto-Δ^2-dihydrothiazine. The isolation of 3,4-dimercaptobutanol was also complicated by cyclodehydration with formation of what is believed to be 3-mercaptotetrahydrothiophene.

Although dimercaptopropionaldehyde could not be expected to be stable, because of the reactivity of the aldehyde group with the dithiol group, its diethyl acetal was prepared in 90% yield and 92% purity using the sodium hydrosulfide technique. Upon standing at room temperature, the acetal group reacted with the dithiol group with liberation of ethanol to form a polymercaptal; within 48 hours this polymer separated from the purest samples. The sulfur analog of this acetal (2,3-dimercaptopropionaldehyde diethyl mercaptal) could not be prepared by the usual methods because of the instability of the intermediate dibromide; however, reaction of dimercaptopropionaldehyde diethyl acetal with ethyl mercaptan in the presence of acidic catalysts yielded, through mercaptan-acetal interchange, the desired compound. Its instability precluded its biologic evaluation.

Interesting compounds were obtained by modification of BAL and a number of its analogs through formation of derivatives by reaction of the mercapto groups with various reagents. Of the several types examined in this work, stable mercaptoles prepared from acetone and the dithiol are described in this paper. Therapeutic results indicated that the active function, thus covered, was not hydrolyzed *in vivo* and consequently was not available for reaction with the metallic poisons. Use of these compounds was therefore limited to stabilizing the labile dithiol structure while other synthetic operations, ordinarily too drastic, were performed as an attempted route to new dithiols.

EXPERIMENTAL PART

2,3-Dimercaptopropyl acetate. One hundred grams (0.805 mole) of 2,3-dimercaptopropanol (BAL) containing 2 drops of conc'd sulfuric acid in 2 ml. of glacial acetic acid was stirred and maintained at 20–30° by external cooling while 87 g. (0.85 mole) of acetic anhydride was added dropwise during the course of forty-five minutes. The mixture was then heated at 60° for one hour, cooled, and allowed to stand for twenty hours. The crude product was washed with three portions of 250 ml. each of water using ether to break the emulsion. The ether solution was dried over sodium bicarbonate and calcium sulfate and distilled at 0.2–0.3 mm. (bath temperature 125–137°) to yield 94 g. of a colorless oil. This was fractionated through a 20-inch packed column to yield 51 g. (38%) of 2,3-dimercaptopropyl acetate boiling at 90°/1.5 mm. This acetate is a colorless, mobile liquid with a sharp, penetrating odor. It is soluble to the extent of about 1 g. in 100 g. of water, and hydrolyzes rapidly in water. Analyses and physical properties of this compound are given in Table I.

2,3-Dimercaptopropyl propionate. By the same procedure as that described above, 200 g. (1.61 moles) of 2,3-dimercaptopropanol containing 5 drops of conc'd sulfuric acid in 5 ml. of propionic acid was reacted with 260 g. (2.0 moles) of propionic anhydride to give 55 g. (19%) of 2,3-dimercaptopropyl propionate, b.p. 70°/0.2 mm.

2,3-Dimercaptopropyl butyrate. Similarly, 124 g. (1.0 mole) of 2,3-dimercaptopropanol, 7 drops of conc'd sulfuric acid in 5 ml. of butyric acid and 190 g. (1.20 moles) of butyric anhydride were reacted to yield 58 g. (30%) of 2,3-dimercaptopropyl butryate, b.p. 77–78°/0.25 mm.

2,3-Dimercaptopropionaldehyde diethyl acetal. Dibromopropionaldehyde and its diethyl acetal were prepared in 89% and 93% yields respectively following the directions of Grard (7).

Into a 1-liter stainless steel autoclave was charged 150 g. of dibromopropionaldehyde diethyl acetal and a sodium hydrosulfide solution prepared by dissolving 37 g. of sodium in 500 ml. of methanol and saturating the resulting solution at 0° with hydrogen sulfide. The mixture was then shaken under hydrogen sulfide pressure for forty-eight hours at room temperature. The solution was transferred to a 2-liter separatory funnel and saturated with carbon dioxide until the *p*H of the solution was reduced to about 8. The precipitated sodium bicarbonate was dissolved by agitating the solution with 1000 ml. of water, and the oil which separated was extracted with ether. The combined ether extracts were dried over calcium sulfate and after removal of the drying agent, the ether was distilled, leaving a pale yellow oil which analyzed for 29.9% thiol sulfur as compared with 32.68% calculated for dimercaptopropionaldehyde diethyl acetal.

Flash distillation of small portions of the crude acetal served to raise this thiol value slightly. However, polymerization occurred with considerable loss of material. For example, 25 g. of residue remaining after the removal of ether was distilled through a short-path still head at 0.25 mm. from a pot held at 110°. Seventeen grams of distillate was collected which analyzed for 31.2% thiol sulfur or a purity of 95.4% assuming the desired acetal to be the only sulfur component present. Analyses for this fraction are given in Table I.

Upon standing at room temperature for several days, distilled and crude samples of this derivative were observed to separate into two layers; the more viscous layer eventually (two months) became opaque and solid. No odor of hydrogen sulfide was detected in the closed container. The upper layer proved to be ethanol, and the mechanism of decomposition seems clearly to be acetal-mercaptal interchange.

2,3-Dimercaptopropionaldehyde diethyl mercaptal. Attempts to prepare this derivative by the thiolation of the dibromide failed because of the instability of the latter, therefore the following method was used.

Thirty-two grams of dimercaptopropionaldehyde diethyl acetal (92% pure by thiol sulfur analysis) was dissolved in 100 g. of ethyl mercaptan and cooled to −30°. One-half ml. of conc'd hydrochloric acid was added, and after standing at this temperature for one-half hour the mixture was allowed to warm up to 25°. After standing overnight at room temperature the excess ethyl mercaptan was removed by evaporation in a stream of nitrogen. The residue was washed with water and then dried over sodium sulfate. The mercaptal was transferred to a small Claisen flask and distilled at 0.5 mm. Thirteen grams of viscous liquid containing suspended water was collected at 70–100°. The water was removed with sodium sulfate. All attempts to purify this product failed; the analysis in Table I was made on the dried distillate above.

3,4-Dimercaptobutanol. Allyl carbinol was prepared as described by Gilman (8). Bromination of allyl carbinol in chloroform yielded 77% of 3,4-dibromobutanol, b.p. 72–74°/4 mm. (9).

Into a 1-liter stainless steel autoclave was charged 120 g. (0.517 mole) of 3,4-dibromobutanol and a solution of sodium hydrosulfide prepared by dissolving 35 g. of sodium in 500 ml. of methanol and saturating the solution with hydrogen sulfide at 0°. The mixture was heated at 40° for forty hours under a hydrogen sulfide pressure of 135 lb./sq. in. The solution was discharged and acidified with 60 ml. of conc'd hydrochloric acid and the precipitated salt removed. After removal of the methanol by distillation under reduced pressure, the residue, consisting of an oil and suspended salt, was shaken with 100 ml. of water and the organic layer separated. The aqueous layer was extracted twice with ether and these

TABLE I

Properties of Some Vicinal Dithiols

NAME	FORMULA	PHYSICAL PROPERTIES				ANALYSIS								Others
						C		H		S		S(H)[b]		
		M.P.[a]	B.P.	d_4^{25}	n_D^{25}	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	
2,3-Dimercaptopropyl acetate	$C_5H_{10}O_2S_2$		90°/1.5 mm.	1.1916	1.5185	36.10	35.4	6.00	6.25	38.60	39.02	38.60	38.20	
2,3-Dimercaptopropyl propionate	$C_6H_{12}O_2S_2$		70°/0.2 mm.	1.1491	1.5089	39.98	40.10	6.66	7.05	35.57	35.53	35.57	35.70	
2,3-Dimercaptopropyl butyrate	$C_7H_{14}O_2S_2$		77–78° 0.25 mm.	1.1095	1.5029	43.28	43.18	7.26	7.45	33.01	32.85	33.01	32.85	
Ammonium 2,3-dimercapto-propionate	$C_3H_9NO_2S_2$	80–85° (dec.)				23.21	23.70	5.84	5.99	41.31	40.50	41.31	41.30	N (Calc'd) 9.02 N (Found) 8.89
2,3-Dimecaptopropylurea	$C_4H_{10}N_2OS_2$	79–81°				28.90	28.77	6.03	6.19	38.57	36.71	38.57	34.40	N (Calc'd) 16.85 N (Found) 16.23
2,3-Dimercaptopropylure-than	$C_6H_{13}NO_2S_2$		129–131° 1.1 mm.	1.1924	1.5277	36.91	36.94	6.72	6.98	32.82	31.99	32.82	32.80	N (Calc'd) 7.17 N (Found) 7.58
3,4-Dimercaptobutanol	$C_4H_{10}OS_2$		96–97°/ 1 mm.	1.1842	1.5583	34.73	35.25	7.29	7.52	46.35	45.97	46.35	45.90	
2,3-Dimercaptopropional-dehyde diethyl acetal	$C_7H_{16}O_2S_2$		dec.			43.09	43.15	8.15	8.01	32.68	31.00	32.68	31.20	
2,3–Dimercaptopropional-dehyde diethyl mercaptal	$C_7H_{16}S_4$		dec.							56.16	49.94	28.08	28.08	

[a] Uncorrected.

[b] Samples of the thiol were titrated in 95% alcohol with 0.1 *N* I_2 (aq.).

extracts combined with the organic layer. Analysis of an aliquot of this solution indicated the presence of 40 g. (58% theory) of dithiol. The ether was removed by distillation at atmospheric pressure and the product was given a primary distillation, two cuts being collected; one at 40–50°/2.5 mm. and another at 80–100°/1.5 mm. The latter 30 g. was redistilled in a 24″ ring-packed column to give 18 g. of pure product boiling at 96–97°/1 mm. The lower-boiling fraction obtained above was redistilled and the main fraction, b.p. 68°/5 mm. had the following analysis:

Found: C, 39.92, 40.15; H, 6.76, 6.73; S, 51.27; S(H), 26.2.

The dehydration product of 3,4-dimercaptobutanol would have the following analysis:

Calc'd for $C_4H_8S_2$: C, 39.95; H, 6.66; S, 53.35; S(H), 26.68.

No further characterization of the products was made to determine whether 3-mercaptotetrahydrothiophene or 2-(mercaptomethyl)propylene sulfide resulted from the dehydration.

2,3-Dimercaptopropylurethan. Allylurethan was prepared from allylamine and ethyl chloroformate as described by Bergmann (10). The dibromide was obtained in 87% yield as a low-melting (40–44°) white solid.

A 1-liter stainless steel autoclave was charged with 188 g. (0.65 mole) of 2,3-dibromopropylurethan and a sodium hydrosulfide solution prepared by dissolving 46 g. (2 g.-atoms) of sodium in 450 ml. of methanol and saturating the solution with hydrogen sulfide. The solution was shaken at room temperature for sixteen hours under a hydrogen sulfide pressure of 100 lb./sq.in. After discharging, the solution was acidified with conc'd hydrochloric acid, and the solvent removed by distillation under reduced pressure. The residue of salt and oil was taken up in 200 ml. of water and extracted three times with ether. After drying the ether extracts, the ether was removed and the product distilled in a 4″ Vigreux column. Eighty-four grams (65%) of product was collected at 129–131°/1.1 mm. Redistillation in a 24″ ring-packed column gave a product with the analyses listed in Table I.

2,3-Dimercaptopropylurea. Dibromopropylurea was prepared according to the method of Taal and Henpel (11). A sodium hydrosulfide solution, prepared by dissolving 41 g. of sodium in 500 ml. of methanol and saturating the solution with hydrogen sulfide at 0°, was charged into a 1-liter Parr bomb with 150 g. of dibromopropylurea. The bomb was agitated under a hydrogen sulfide pressure of 50–75 lb./sq. in. at room temperature for fifty hours and then at 50–60° for an additional two hours. The reaction mixture was acidified with 50 ml. of conc'd hydrochloric acid, and the precipitated salt filtered off. After removing the solvent under reduced pressure at a bath temperature of not more than 60°, the residue of salt and moist product was taken up in 500 ml. of ethyl acetate and 300 ml. of water. The organic solvent layer titrated for 55 g. of dithiol and the water layer for 17 g., assuming only one species to be present. The water layer was extracted four times with a total of 500 ml. of ethyl acetate. This reduced the thiol content to an equivalent of 2.5 g. of dithiol in the aqueous layer. The combined extracts were dried over calcium sulfate, and the solvent removed at reduced pressure. The residue consisted of a pale, pink, viscous syrup, and weighed 85 g. Thiol analysis indicated a purity of 84%.

The impure oil was shaken under nitrogen with 800–850 ml. of warm (35–40°) distilled water; the solution was cooled to room temperature and allowed to settle. The cloudy solution was decanted from undissolved oil (18 g.), shaken with 20 g. of acid-extracted kieselguhr, and filtered by suction. The clear filtrate was rapidly stirred while cooling in a mixture of Dry-Ice-methanol until it solidified. The solid cake containing crystals of the desired product in fine dispersion was allowed to warm up to the melting point, and the crystals removed. Thirty-six grams of product was obtained which analyzed for 36.2% thiol sulfur, corresponding to a purity of 94%. Analyses are given in Table I.

Further purification of 2,3-dimercaptopropylurea was not generally possible, although crystallization of small amounts was effected in isolated cases. A sample which analyzed for 99% of the theoretical thiol sulfur (m.p. 79–81°) was obtained from ethanol-ether mixtures but when this technique was applied to the purification of larger or less pure samples, only oils were obtained.

The synthesis of 2,3-dimercaptopropionic acid and its methyl ester is outlined elsewhere (5). Several derivatives of these compounds not previously described are as follows:

4-Carboxy-2,2-dimethyl-1,3-dithiolane was prepared by refluxing 15 g. of the 2,3-dimercaptopropionic acid in 100 ml. of dry acetone for 0.5 hour. After removal of excess acetone, the product was distilled, b.p. 121–122°/1.5 mm., or crystallized directly from petroleum ether (b.p. 30–75°) to yield 18 g. (93%), m.p. 51–53°. Neut. equivalent, calc'd: 178.3; found, 182.

4-Carbomethoxy-2,2-dimethyl-1,3-dithiolane, the acetone mercaptole of methyl 2,3-dimercaptopropionate was prepared by mixing 114 g. of methyl 2,3-dimercaptopropionate and 46 g. of acetone, cooling to 0° in an ice-bath, and saturating the solution with dry hydrochloric acid. An aqueous layer separated and was removed after the solution had warmed to room temperature. The product was washed twice with water and then with dilute sodium bicarbonate solution. After drying, it was distilled through a 4″ Vigreux column, b.p. 73–74°/0.5 mm., yield 110 g. (82%). By reaction with ammonia in alcohol solution, this derivative was converted into the corresponding amide, *4-carbamyl-2,2-dimethyl-1,3-dithiolane*, m.p. 89–90°.

Anal. Calc'd for $C_6H_{11}NOS_2$: C, 40.68; H, 6.23; S, 36.17; N, 7.90.
Found: C, 40.14; H, 6.75; S, 36.75; N, 7.87.

This amide was also prepared from 4-carboxy-2,2-dimethyl-1,3-dithiolane (above) by reaction of 12 g. (0.087 mole) with 2.6 g. (0.044 mole) of urea at 160–170° for one hour. The resultant viscous mass was crystallized from benzene to yield 3 g. (25%) of product, m.p. 89–90°. There was no depression of the melting point when this compound was mixed with the 4-carbamyl-2,2-dimethyl-1,3-dithiolane prepared from the ester (above).

Ammonium 2,3-dimercaptopropionate. Thirty-five grams of dimercaptopropionic acid was dissolved in 200 ml. of ether and cooled to 0°. Ammonia gas was bubbled into the solution until no further precipitation occurred. One-half of the ether was removed by evaporation on a steam-bath and enough absolute alcohol was added (about 120 ml.) to just dissolve all the solid. On cooling, the product crystallized as white flakes; these were filtered off and dried *in vacuo* yielding 36 g. (93%) of slightly hygroscopic crystals which melted (with decomposition) between 80° and 85°. See Table I for analyses.

SUMMARY

1. A number of vicinal dithiols, analogs of BAL (British Anti-Lewisite), have been prepared and their properties recorded.

2. Several new derivatives of vicinal dithiols are reported.

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