108. 2 : 3-*Dimercaptopropanol* (" *British Anti-Lewisite* ") *and Related Compounds.*

By L. A. STOCKEN.

The preparation of several aliphatic dithiols and in particular of pure 2 : 3-dimercaptopropanol is described, together with their condensation products with carbonyl compounds and dichloroarsines.

FUNDAMENTAL work on the reaction between arsenical compounds and proteins (Stocken and Thompson, 1940, Report to the Ministry of Supply by Peters, No. 20) suggested that the toxicity of arsenic to living cells is due to its combination with two neighbouring thiol groups in an essential enzyme to form a stable ring. The consequence of this hypothesis was the possibility that 1 : 2- or 1 : 3-dithiols might displace arsenic from tissue receptors by giving more stable five- or six-membered rings and would thus constitute antidotes to arsenical war gases. Preliminary experiments with toluene-3 : 4-dithiol and ethanedithiol indicated that this type of compound was indeed capable of affording effective protection *in vitro* and *in vivo* against the toxic action of " lewisite'". It was found, however, that neither of these substances satisfied certain conditions desirable in an antidote for field application against skin contamination, and it was necessary, therefore, to prepare other compounds having 1 : 2- or 1 : 3-dithiol

substitution. For reasons explained elsewhere (Stocken and Thompson, *Biochem. J.*, 1946, **40**, 535) the search was confined to compounds of low molecular weight and preferably to those which had a hydrophilic group. Since, in the event of equal therapeutic efficiency, the final choice of antidote depended on toxicity, a few typical compounds were synthesised with the hope of making generalisations about their properties. From this work it seemed that aryl- and 1 : 3-dithiols were the least satisfactory and that 2 : 3-*dimercaptopropanol* (subsequently called " British Anti-Lewisite " or " BAL ") was sufficiently superior to the others to justify its manufacture on a large scale.

Of the many methods available for the preparation of thiols, only the reaction between the halogen compound and ammonium or metal hydrogen sulphide gave good results when applied to the production of dithiols. Even this reaction was unsatisfactory unless a closed system was used to avoid sulphide formation (cf. Meadow and Reid, *J. Amer. Chem. Soc.*, 1934, **56**, 2177), and 2 : 3-dimercaptopropylamine could only be obtained by means of ammonium hydrogen sulphide. The use of this sulphide for the preparation of thiols is apparently new, and it possesses certain advantages over the metal hydrogen sulphides. Ammonium hydrogen sulphide is more soluble (20% in methanol), the excess remaining at the end of the reaction is conveniently removed by evacuation of the vessel, and the product is much cleaner. In the preparation of BAL several variants of the hydrogen sulphide process were tried, but since a more detailed investigation was subsequently carried out by Gasson, Millidge, Woodward, *et al.* (Sutton Oak reports 1942 and 1943) only the two most effective are described here.

Although the analytical figures indicated that only a small amount of impurity could be present, some evidence gained from the preparation of acetals suggested that laboratory specimens of BAL were not absolutely pure. A further purification was effected by partition between water and an excess of the dithiol, but the efficacy of the method was not reflected by any significant change in the analytical figures. It was considered, therefore, that some supplementary test was required, especially when a sample from the U.S.A. (prepared by a catalytic process and having satisfactory analytical figures) was found to be unduly toxic. Chromatography gave no indication of the presence of a contaminant in the water-purified BAL which was used as a standard. A comparison of the physical constants of preparations obtained from four sources (see Table) revealed little or no difference in refractive index or density but did show a significant difference in viscosity and solubility in water. Subsequent to the completion of this work Sjöberg (*Ber.*, 1942, **75**, 13) described the preparation of 2 : 3-dimercaptopropanol, which he purified by means of the mercury derivative. The dithiol was then distilled at low pressure, to give an overall yield of 14%.

Physical constants of various specimens of 2 : 3-*dimercaptopropanol at* 20°.

	d.	n_D.	η.*	Solubility (w/v, %).
I.C.I. preparation (semi-large scale)	1·2578	1·5749	1·494	5·9
U.S.A. catalytic preparation	1·2427	1·5767	0·7333	5·6
Sutton Oak (laboratory preparation)	1·2472	1·5749	1·018	6·4
Oxford (purified)	1·2463	1·5733	1·000	6·8

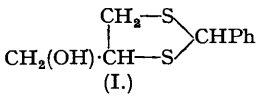
* Relative to purest Oxford sample.

Unfortunately, the hydrogen sulphide method cannot be applied when other reactive substituents are present. An attempt was therefore made to protect the dithiol groups, to carry out further synthetic steps, and then as a final stage to regenerate the thiol. Thioacetals were prepared, but at the time this work was reported to the Ministry of Supply (Stocken, Thompson, and Whittaker, 1942, Report to Ministry of Supply by Peters, No. 52; Stocken and Thompson, 1943, Report to Ministry of Supply by Peters, No. 64) no success had been achieved. More recently, however, it has been found that 2 : 3-*bisbenzylthiopropanol*, 2-*phenyl*-4-*hydroxymethyl*-1 : 3-*dithiolan* (I), and 2-*methyl*-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (II) can be reduced in the presence of ethanol by sodium in liquid ammonia to give excellent yields of 2 : 3-dimercaptopropanol.

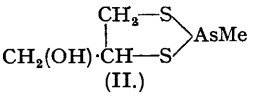
In view of the structural similarity of 2 : 2′-dichlorodiethyl sulphide (" mustard gas ") to 2-*methyl*-4-*chloromethyl*-1 : 3-*dithiolan* and 2 : 2-*dimethyl*-4-*chloromethyl*-1 : 3-*dithiolan*, it was expected that these compounds might possess some vesicant power, but they were found to have only 2% and 1% of the absolute vesicancy of mustard gas.

Since only two cyclic thioarsinites have so far been described (Cohen, King, and Strangeways, *J.*, 1931, 3043), both of which were derived from ethanedithiol, 2-chlorovinyl-, phenyl-, and methyl-dichloroarsines were condensed with the 1 : 2- and 1 : 3-dithiols, the latter giving rise to 1 : 3-*dithia*-2-*arsa*cyclo*hexane* (III).

An attempt made to prepare the open chain thioarsinites from bis-2-chlorovinylchloroarsine and the dithiols was abandoned, since the products decomposed on distillation.



(I.)



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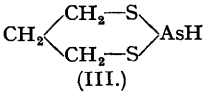

(III.)

Experimental.

The sodium hydrogen sulphide solution was prepared by dissolving sodium (5 g.) in ethanol (100 c.c.) and saturating with dry hydrogen sulphide at 0—5°, and the ammonium hydrogen sulphide by passing dry ammonia and hydrogen sulphide into ether (sodium dried) at 0°.

Ethane-, 1 : 2-*Propane-*, 1 : 3-*Propane- and* 1 : 5-*Pentane-dithiols.*—The appropriate dihalide (1 mol.) was heated with sodium hydrogen sulphide (6 mols.) in ethanol for 12 hours in a closed vessel at 80—90°. Since these dithiols distil with the ethanol, 10N-sodium hydroxide (6 mols.) was added to the reaction product before evaporation of the ethanol under reduced pressure. The residue was then acidified to Congo-red with hydrochloric acid (external cooling), and sodium chloride was removed by filtration. The dithiol which separated was combined with a single ether extract of the aqueous layer, dried (Na_2SO_4), and, after removal of the solvent, distilled. The yields were 55—65%.

1 : 3-*Dimercaptopropanol.* 1 : 3-Dibromohydrin (0·1 mol.) was heated at 80—90° with sodium hydrogen sulphide (0·6 mol.) in ethanol for 12 hours in a pressure bottle. After acidification of the reaction mixture the ethanol was removed under reduced pressure, and sufficient water added to dissolve the sodium chloride; chloroform was used to extract the dithiol. Yield, 65%; b. p. 80°/1·0 mm. Rheinboldt and Tetsch (*Ber.*, 1937, **70**, 675) give b. p. 94°/12 mm. in a stream of carbon dioxide (Found: S, 51·4; SH, 53·0. Calc. for $C_3H_8OS_2$: S, 51·6; SH, 53·2%). Propane-1 : 2 : 3-trithiol was prepared similarly. Yield, 50%; b. p. 95°/1·0 mm. (Found: SH, 70·8. Calc. for $C_3H_8S_3$: SH, 70·8%).

2 : 3-*Dimercaptopropylamine.* 2 : 3-Dibromopropylamine hydrochloride (40 g.) was heated in a pressure bottle with ammonium hydrogen sulphide (120 g. in 600 c.c. of methanol) for 16 hours at 80—90°. The excess of hydrogen sulphide and alcohol was then removed under reduced pressure, and the residue was taken up in the minimum volume of dilute ammonia. The solution was then extracted many times with benzene. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was distilled at low pressure. Yield, 8 g. (40%), b. p. 80°/1·0 mm. (Found: S, 52·3. $C_3H_9NS_2$ requires S, 52·0%).

Methyl 2 : 3-*dimercaptopropyl ether* was obtained from methyl 2 : 3-dibromopropyl ether by the method described for 1 : 3-dimercaptopropanol. Yield, 50%; b. p. 68°/1·0 mm. (Found: S, 46·0. $C_4H_{10}OS_2$ requires S, 46·4%).

2 : 3-*Dimercaptopropanol* (" *British Anti-Lewisite* "). 2 : 3-Dibromohydrin (1 kg.) was allowed to react for several days at room temperature with sodium hydrogen sulphide solution (12·6 l.) in a closed vessel filled to capacity. The usual process was employed for the isolation of the *compound.* Yield, 366 g. (64%). There was no significant alteration in yield when the alternative higher temperature method was used, but the available apparatus limited the absolute yield to about 26 g.

" Crude " 2 : 3-dimercaptopropanol (360 g.) was shaken with distilled water (4 l.) for 3 hours at room temperature, and then allowed to settle overnight. The supernatant layer was filtered through two No. 1. Whatman filter papers to remove oily globules; ammonium sulphate (1900 g.) was added to the filtrate which was then extracted with benzene (1 l.) (Stocken and Thompson, 1943, Report to Ministry of Supply by Peters, No. 65; Peters, Stocken and Thompson, Report to Ministry of Supply by Peters, No. 77). The benzene extract was dried (Na_2SO_4), filtered, evaporated under reduced pressure (40—50°), and the residue distilled in a high vacuum. The middle 80% was taken for examination although there was neither a low- nor a high-boiling fraction. This experiment was repeated several times in order to obtain 1 l. of a standard preparation (Found: C, 28·6 *; H, 6·53 *; S, 51·7; SH, 53·5. $C_3H_8OS_2$ requires C, 29·0; H, 6·55; S, 51·6; SH, 53·2%).

Condensation Products of Dithiols with Carbonyl Compounds.—2 : 3-Dimercaptopropanol (124 g.) mixed with benzaldehyde (106 g.) in benzene (300 c.c.) and a few drops of concentrated hydrochloric acid reacted exothermically to give 2-*phenyl*-4-*hydroxymethyl*-1 : 3-*dithiolan* which was isolated after removal of water by crystallisation from benzene–light petroleum (b. p. 60—80°). Yield, 200 g.; m. p. 77°; b. p. 207°/1·5 mm. (slight decomp.) (Found: S, 30·4. $C_{10}H_{12}OS_2$ requires S, 30·2%). Benzaldehyde and 1 : 3-dimercaptopropanol were condensed in the same way as described for the isomer and the 2-*phenyl*-4-*hydroxy*-1 : 3-*dithian* crystallised from benzene. Yield, almost quantitative; m. p. 142—143° (Found: S, 30·3. $C_{10}H_{12}OS_2$ requires S, 30·2%). 2-Phenyl-4-hydroxymethyl-1 : 3-dithiolan (212 g.) was refluxed with thionyl chloride (145 g.) in benzene (500 c.c.) until no more hydrogen chloride was evolved. The solution was then evaporated, and the residue distilled, at low pressure. Yield, 140 g. of 2-*phenyl*-4-*chloromethyl*-1 : 3-*dithiolan*; b. p. 150°/0·8 mm.; m. p. 69—70° (Found: S, 27·6; Cl, 15·6. $C_{10}H_{11}ClS_2$ requires S, 27·8; Cl, 15·4%). 2-Phenyl-4-chloromethyl-1 : 3-dithiolan (23 g.) was refluxed for 6 hours with potassium cyanide (7·0 g.) and sodium iodide (0·2 g.) in methanol (200 c.c.). The product was worked up in the usual way. Yield, 16 g. of 2-*phenyl*-4-*cyanomethyl*-1 : 3-*dithiolan*; b. p. 180°; m. p. 69° (Found: S, 28·8. $C_{11}H_{11}NS_2$ requires S, 29·1%). 2 : 3-Dimercaptopropanol (124 g.) and acetaldehyde (45 g.) were refluxed for 3 hours in benzene (200 c.c.) with the addition of a few drops of hydrochloric acid as a catalyst. After evaporation of the solvent the residue was distilled at low pressure. Yield, 98 g. of 2-*methyl*-4-*hydroxymethyl*-1 : 3-*dithiolan*; b. p. 115°/0·8 mm.; m. p. 57—58° (Found: S, 42·9. $C_5H_{10}OS_2$ requires S, 42·7%). 2-Methyl-4-hydroxymethyl-1 : 3-dithiolan (30 g.) was converted into 2-*methyl*-4-*chloromethyl*-1 : 3-*dithiolan* by heating with thionyl chloride (22 g.) in benzene (100 c.c.). Yield, 23 g.; b. p. 94°/2·0 mm. (Found: S, 37·7; Cl, 20·8. $C_5H_9ClS_2$ requires

* Analyses by Mr. F. Hall, Dyson Perrins laboratory.

S, 38·0; Cl, 21·1%). Acetone (29 g.) and 2 : 3-dimercaptopropanol (62 g.) were condensed in the usual way to give 2 : 2-*dimethyl*-4-*hydroxymethyl*-1 : 3-*dithiolan* (54 g.) which was crystallised from benzene–light petroleum (b. p. 40—60°); b. p. 105°/1·0 mm.; m. p. 54—55° (Found: S, 39·2. $C_6H_{12}OS_2$ requires 39·0%). 2 : 2-*Dimethyl*-4-*chloromethyl*-1 : 3-*dithiolan* was obtained in 72% yield by the method already described; b. p. 80°/0·7 mm. (Found: S, 35·5; Cl, 19·2. $C_6H_{11}ClS_2$ requires S, 35·1; Cl, 19·4%). 2 : 3-Dimercaptopropanol (124 g.) and *cyclo*hexanone (98 g.) in benzene (200 c.c.) in the same way gave 2 : 2-*pentamethylene*-4-*hydroxymethyl*-1 : 3-*dithiolan* (130 g.); b. p. 150°/0·8 mm.; m. p. 70° (Found: S, 31·7. $C_9H_{16}OS_2$ requires S, 31·4%).

Condensation Products of Dithiols with Dichloroarsines.—The various dithiols and the arsenical compounds were all condensed in the same way. The arsenical compound (0·05 mol.) in chloroform (100 c.c.) was slowly added to a solution of dithiol (0·05 mol.) and pyridine (0·1 mol.) in chloroform (60 c.c.) at 0—5°. The chloroform solution was washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and filtered, and after evaporation of the chloroform the residue was distilled at low pressure. 4-*Hydroxymethyl*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 65%) had b. p. 165°/0·2 mm. (Found: S, 24·6; Cl, 13·8; As, 28·17. $C_5H_8OClS_2As$ requires S, 24·7; Cl, 13·7; As, 29·0%). 2-*Phenyl*-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* was not distilled but crystallised from benzene; yield, 65%; m. p. 97—98° (Found: S, 23·5; As, 27·0. $C_9H_{11}OS_2As$ requires S, 23·3; As, 27·3%). 2-*Methyl*-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 70%) had b. p. 158°/1·5 mm. (Found: S, 30·3. $C_4H_9OS_2As$ requires S, 30·2%). 4-*Methyl*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield 75%) had b. p. 127°/0·6 mm. (Found: S, 26·6; Cl, 14·5; As, 30·7. $C_5H_8ClS_2As$ requires S, 26·4; Cl, 14·6; As, 30·9%). 2-(2-*Chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 56%) had b. p. 120°/0·4 mm.; on standing it slowly crystallised; m. p. 35° (Found: S, 28·3; Cl, 15·7; As, 33·2. $C_4H_6ClS_2As$ requires S, 28·0; Cl, 15·5; As, 32·8%). 4-*Methoxymethyl*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*pentane* (yield, 78%) had b. p. 145°/0·6 mm. (Found: S, 23·8; Cl, 12·9; As, 27·3. $C_6H_{10}OClS_2As$ requires S, 23·5; Cl, 13·0; As, 27·4%). 5-*Hydroxy*-2-(2-*chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*hexane* (yield, 65%) had b. p. 160°/0·8 mm. (Found: S, 24·8; Cl, 13·9; As, 29·5. $C_5H_8OClS_2As$ requires S, 24·7; Cl, 13·7; As, 29·0%). 5-*Hydroxy*-2-*phenyl*-1 : 3-*dithia*-2-*arsa*cyclo*hexane* (yield, 60%) had b. p. 190°/1·0 mm. (Found: S, 23·3; As, 27·8. $C_9H_{11}OS_2As$ requires S, 23·3; As, 27·3%). 2-(2-*Chlorovinyl*)-1 : 3-*dithia*-2-*arsa*cyclo*hexane* (yield, 59%) had b. p. 150°/0·4 mm. (Found: S, 26·8; Cl, 14·7; As, 30·8. $C_5H_8ClS_2As$ requires S, 26·4; Cl, 14·6; As, 30·9%). A solution of *p*-carboxyphenyldichloroarsine (26·7 g.) in chloroform (300 c.c.) was added to 2 : 3-dimercaptopropanol (12·4 g.) and pyridine (16 c.c.) in chloroform (100 c.c.). On the addition of 2N-hydrochloric acid to remove pyridine, 2-(p-*carboxyphenyl*)-4-*hydroxymethyl*-1 : 3-*dithia*-2-*arsa*cyclo*pentane* separated. The product was filtered off, and washed with N-hydrochloric acid and finally water; it was then crystallised from ethanol giving 23 g.; m. p. 178—180° (Found: S, 19·6. $C_{10}H_{11}O_3S_2As$ requires S, 20·1%). The *brucine* salt had m. p. 203—206° (decomp.) (Found: S, 9·0. $C_{33}H_{37}O_7N_2S_2As$ requires S, 9·0%).

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