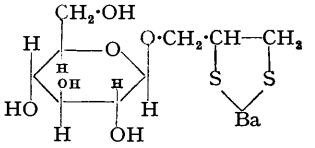
# 60. *Dithiols. Part II. 2 : 3-Dimercaptopropyl Ethers of Glycerol and of Glycollic Acid, with some Further Observations on "BAL-Intrav."*

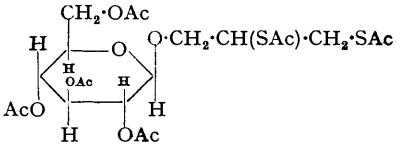
By R. M. Evans and L. N. Owen.

The preparation of crystalline *hexa-acetyl* β-(2′ : 3′-*dimercaptopropyl*)*glucoside*, and of the liquid *α-isomer*, is described. The α- and β-2 : 3-*dimercaptopropyl ethers* of glycerol, and the 2 : 3-*dimercaptopropyl ether* of glycollic acid have been synthesised *via* the corresponding allyl ethers. An attempt to prepare γδ-dimercaptovaleric acid resulted in the formation of the γ-S-*lactone* of this substance.

During the earlier part of the recent war, the investigations of a group of workers at Oxford led to the development of 2 : 3-dimercaptopropanol (British Anti-Lewisite; "BAL") as an effective antidote for arsenical poisoning (Stocken and Thompson, *Biochem. J.*, 1946, **40**, 535; Stocken, *J.*, 1947, 592); more recently it has been found effective also in cases of poisoning by mercury, cadmium, and gold (see, *inter al.*, *J. Pharmacol.*, 1946, **87**, 85, 102, 119; *Science*, 1946, **104**, 220; *J. Amer. Med. Assoc.*, 1947, **133**, 749). When admistered internally, however, BAL itself is somewhat toxic, and in 1943 Dr. J. F. Danielli, then of the Department of Biochemistry, University of Cambridge, pointed out that water-soluble derivatives of BAL, containing the 1 : 2-dithiol structure with several additional polar groups, would be expected to show diminished toxicity, whilst retaining the anti-arsenical activity of the parent compound. The β-glucoside ("BAL-Intrav") was accordingly synthesised by one of us in the form of its barium salt (I), and when tested biologically it proved to be highly effective and of extremely low toxicity (Danielli, Danielli, Fraser, Mitchell, Owen, and Shaw, *Biochem. J.*, 1947, **41**, 325).*




(I.)




(II.)

At that time the intermediate hexa-acetate (II) of BAL-Intrav was obtained only as a syrup, by the action of potassium thiolacetate on 2 : 3 : 4 : 6-tetra-acetyl β-(2′ : 3′-dibromopropyl)glucoside, but a more recent preparation partly crystallised, and it was possible, by recrystallisation from ethanol, to obtain analytically pure 2 : 3 : 4 : 6 : 2′ : 3′-*hexa-acetyl* β-(2′ : 3′-*dimercaptopropyl*)*glucoside* (II), m. p. 75—77°. In Part I (*loc. cit.*), the preparation was also described of BAL-Intrav hexa-acetate from a tetra-acetyl allylglucoside consisting largely of the α-form. In view of the isolation of the crystalline β-hexa-acetate, BAL-Intrav hexa-acetate has now been synthesised from pure tetra-acetyl α-allylglucoside (readily prepared by isomerisation of the β-isomer with titanium tetrachloride). Addition of bromine to the tetra-acetate gave 2 : 3 : 4 : 6-*tetra-acetyl* α-(2′ : 3′-*dibromopropyl*)*glucoside*, which reacted with potassium thiolacetate to give *hexa-acetyl* α-(2′ : 3′-*dimercaptopropyl*)*glucoside*, $[\alpha]_D$ + 88°, which has so far resisted all attempts at crystallisation. The difficulty in obtaining these products in crystalline form is probably due to their existence as mixtures of two stereoisomerides owing to asymmetry at position 2′; this condition will obviously arise in all cases where the dibromopropyl and dimercaptopropyl groups are linked to an optically active system.

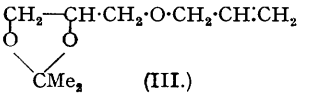
In view of the successful biological tests on the glucoside, it was clearly desirable to synthesise further water-soluble derivatives of BAL, and the present paper describes experiments directed towards the preparation of its ethers with glycerol (both α- and β-) and with glycollic acid. The methods adopted were essentially the same as that used for the synthesis of the glucoside, in that they involved the preparation of the allyl ether, followed by bromination, treatment with potassium thiolacetate to give the acetylated dithiol, and final deacetylation to the dithiol, according to the following general scheme :

$$R\cdot O\cdot CH_2\cdot CH{:}CH_2 \longrightarrow R\cdot O\cdot CH_2\cdot CHBr\cdot CH_2Br \longrightarrow R\cdot O\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot SAc \longrightarrow R\cdot O\cdot CH_2\cdot CH(SH)\cdot CH_2\cdot SH$$

In the cases of the glycerol ethers, the fully acetylated allyl ethers were used, in order to avoid any wandering of acetyl groups in the bisacetylthio-compound.

* The chemical portion of this paper (Fraser, Owen, and Shaw) is considered as Part I of this series.

The starting point for the synthesis of the α-glyceryl ether was 1 : 2-*iso*propylidene glycerol. In order to ensure homogeneity, this was first converted into its crystalline benzoate, which was then treated with allyl bromide in the presence of excess of concentrated aqueous sodium hydroxide (cf. Nichols and Yanovsky, *J. Amer. Chem. Soc.*, 1944, **66**, 1625; 1945, **67**, 46) to give the *α-allyl ether* (III); on hydrolysis with aqueous-alcoholic hydrochloric acid this yielded 2 : 3-*dihydroxypropyl allyl ether* (IV), characterised as the *bisphenylurethane*. The same product was also obtained, more directly, by the action of sodium allyloxide in allyl alcohol on glycerol



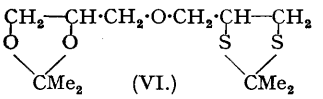
(III.)

$CH_2(OH)\cdot CH(OH)\cdot CH_2\cdot O\cdot CH_2\cdot CH{:}CH_2$

(IV.)

$CH_2(OAc)\cdot CH(OAc)\cdot CH_2\cdot O\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot SAc$

(V.)

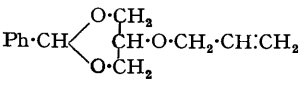


(VI.)

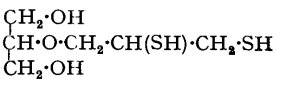
$CH_2(OH)\cdot CH(OH)\cdot CH_2\cdot O\cdot CH_2\cdot CH(SH)\cdot CH_2\cdot SH$

(VII.)

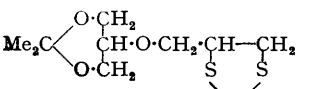
α-chlorohydrin, its identity being confirmed by formation of the same bisphenylurethane. Acetylation with acetic anhydride and sodium acetate gave the *diacetate*, which absorbed bromine in carbon tetrachloride solution to give 2 : 3-*dibromopropyl* 2 : 3-*diacetoxypropyl ether*. With potassium thiolacetate in boiling ethanol this was converted into 2 : 3-*diacetoxypropyl* 2 : 3-*bisacetylthiopropyl ether* (V). This product was deacetylated by treatment with cold aqueous sodium hydroxide under nitrogen, but the material so obtained did not give correct analyses for the expected BAL β-glyceryl ether. The thiol content was considerably less than that of the total sulphur, and a Zerewitinoff determination indicated a deficiency in active hydrogen. On reaction with acetone, however, a *di*iso*propylidene* derivative (VI) was obtained. The product was therefore a mixture containing the required dithiol (VII), together with some



(VIII.)



(IX.)



(X).

by-product, probably formed by intramolecular loss of water or hydrogen sulphide. Easy dehydration of hydroxy-thiols has, indeed, been encountered in several instances (cf. Part III, following paper).

By a similar series of reactions, 1 : 3-benzylidene glycerol (prepared in improved yield) was successively converted into 1 : 3-*benzylidene* 2-*allyl glycerol* (VIII), 1 : 3-*dihydroxy*-2-*propyl allyl ether*, 2 : 3-*dibromopropyl* 1 : 3-*diacetoxy*-2-*propyl ether*, and 1 : 3-*diacetoxy*-2-*propyl* 2 : 3-*bisacetylthiopropyl ether*. In contrast to the (V), deacetylation of this tetra-acetate proceeded normally with aqueous sodium hydroxide to give 1 : 3-*dihydroxy*-2-*propyl* 2 : 3-*dimercaptopropyl ether* (IX). On reaction with acetone it gave a *di*iso*propylidene* derivative (X).

The *allyl ether* (XI) of glycollic acid was synthesised by reaction of chloroacetic acid with

$CH_2{:}CH\cdot CH_2\cdot O\cdot CH_2\cdot CO_2H$

(XI.)

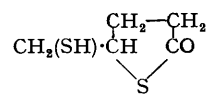
$CH_2(SH)\cdot CH(SH)\cdot CH_2\cdot O\cdot CH_2\cdot CO_2H$

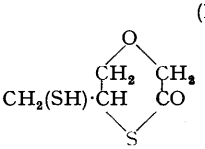
(XII.)

$CH_2(SH)\cdot CH(SH)\cdot [CH_2]_2\cdot CO_2H$

(XIII.)

(XIV.)





(XV.)

sodium allyloxide in allyl alcohol, and was then converted into the *ethyl* ester. The latter was treated with bromine in carbon tetrachloride solution to give the 2 : 3-*dibromopropyl ether* of ethyl glycollate, which with potassium thiolacetate gave the corresponding 2 : 3-*bisacetylthiopropyl ether*. On being stirred with cold aqueous sodium hydroxide this underwent saponification and deacetylation to yield 2 : 3-*dimercaptopropoxyacetic acid* (XII).

If in the last compound the ethereal oxygen atom were eliminated, γδ-dimercaptovaleric acid (XIII) would result. Although not an ether of BAL, this compound still contains the essential dithiol structure, and is of interest as a higher homologue of αβ-dimercaptopropionic acid ("BAL acid") (U.S.P. 2,408,094). Ethyl but-3-ene-1-carboxylate (Zeidler, *Annalen*, 1877, **187**, 39) reacted with bromine to give *ethyl* 3 : 4-*dibromobutane*-1-*carboxylate*, which with potassium

thiolacetate was converted into *ethyl* 3 : 4-*bisacetylthiobutane*-1-*carboxylate*. Treatment of this compound with aqueous alkali and distillation of the product gave the γ-S-*lactone* (XIV), characterised as its α-*naphthylurethane*. On standing in cold aqueous alkali, this lactone was converted into the free dithiol (XIII), since acidification and immediate titration with iodine indicated the presence of two thiol groups, but on attempted isolation the acid reverted to the lactone. This behaviour is not unexpected, since Schjanberg (*Ber.*, 1941, **74**, 1751) has reported the formation of *S*-lactones from γ- and δ-mercapto-acids. It is interesting, however, that the glycollic ether (XII) showed no tendency towards lactonisation, although, from a consideration of bond lengths and valency angles at the ethereal oxygen atom, the formation of a " δ "-lactone (XV), of greater stability than that of a normal *S*-δ-lactone, might have been expected.

## Experimental.

*Determination of Thiol Values.*—SH groups (expressed as " thiol-S ") were determined by titration in acid solution with N/10-iodine, but in order to obtain a sharp end-point and reproducible results (cf. Lucas and King, *Biochem. J.*, 1932, **26**, 2076; Levene, *J. Biol. Chem.*, 1935, **109**, 141) the temperature was kept at 0°, and sufficient hydrochloric or sulphuric acid was added to ensure that the acid concentration was at least N throughout the titration. Starch was used as indicator.

*Hexa-acetyl β-(2′ : 3′-Dimercaptopropyl)glucoside* (II).—Tetra-acetyl β-(2′ : 3′-dibromopropyl)glucoside (38 g.) (Fischer, *Z. physiol. Chem.*, 1920, **108**, 3) and potassium thiolacetate (17 g.), dissolved in ethanol (150 c.c.), were refluxed for 6 hours. The cooled solution was diluted with water (500 c.c.) and extracted with ether. Removal of solvent from the dried extract gave a viscous yellow oil, which when dissolved in ethanol (100 c.c.) and kept at 0° for several days deposited colourless crystals of the *hexa-acetate*, which after recrystallisation from ethanol had m. p. 75—77°, $[\alpha]_D^{18°}$ −26° (*c*, 0·65 in methanol) (Found : C, 46·65; H, 5·6; S, 12·0. $C_{21}H_{30}O_{12}S_2$ requires C, 46·8; H, 5·6; S, 11·9%). Light absorption in alcohol : $\lambda_{max.}$ 2280 A.; $\epsilon$ 8800.

2 : 3 : 4 : 6-*Tetra-acetyl α-Allylglucoside.*—The β-isomer (Fischer, *loc. cit.*) (38 g.) and titanium tetrachloride (20 g.) in pure chloroform (500 c.c.) were refluxed for 2 hours. The solution was then cooled, washed with water and sodium hydrogen carbonate solution, dried, and evaporated to a solid residue, which on recrystallisation from light petroleum (b. p. 60—80°) gave the α-compound (25 g.), m. p. 51—53°, $[\alpha]_D^{15°}$ + 131° (*c*, 1·1 in methanol).

2 : 3 : 4 : 6-*Tetra-acetyl α-(2′ : 3′-Dibromopropyl)glucoside.*—The above tetra-acetate (10 g.) in chloroform (50 c.c.) was treated below 5° with a solution of bromine (4·4 g.) in chloroform (25 c.c.), added gradually during 1 hour. The solution was then washed with sodium hydrogen carbonate, dried, and evaporated to a yellow oil. A portion of this product was purified by chromatography on an alumina column, being transferred to the column in benzene solution and eluted with benzene–ether (1 : 1). Evaporation of the eluate gave a colourless oil, $[\alpha]_D^{20°}$ + 92° (*c*, 1·1 in methanol), consisting essentially of the required *dibromide* (Found : Br, 30·7. $C_{17}H_{24}O_{10}Br_2$ requires Br, 29·2%).

*Hexa-acetyl α-(2′ : 3′-Dimercaptopropyl)glucoside.*—Prepared from the above dibromide (13 g.) and potassium thiolacetate (8 g.) in the same way as for the β-compound, the *compound* was obtained as a yellow oil (12 g.), $[\alpha]_D^{25°}$ + 88° (*c* 1·1 in methanol), which failed to crystallise (Found : S, 11·6. $C_{21}H_{30}O_{12}S_2$ requires S, 11·9%). The thiol value was determined by saponification of a sample with alcoholic 2N-sodium hydroxide at room temperature, followed by acidification and titration with iodine (Found : thiol S, 10·7%).

3-*Allyl Ether of* 1 : 2-iso*Propylidene Glycerol* (III).—The benzoate, m. p. 35°, of 1 : 2-*iso*propylidene glycerol was prepared by the method of Fischer and Pfähler (*Ber.*, 1920, **53**, 1606); a suspension of this compound (65 g.) in 50% aqueous sodium hydroxide (110 c.c.) was vigorously stirred at 75° while allyl bromide (70 g.) was added during 2 hours. The temperature was then raised to 85° for 2 hours, stirring being maintained, and the solution then cooled and extracted with ether. The product so obtained was distilled to yield the *allyl ether*, as a colourless liquid (30 g.), b. p. 87°/22 mm., $n_D^{19°}$ 1·4326 [Found : C, 62·5; H, 9·1; ⌶ (by hydrogenation), 0·97. $C_9H_{16}O_3$ requires C, 62·75; H, 9·35%].

2 : 3-*Dihydroxypropyl Allyl Ether.*—(*a*) A solution of the above compound (50 g.) in ethanol (375 c.c.) and 1% aqueous hydrochloric acid (125 c.c.) was refluxed for 3 hours, then neutralised with barium carbonate, filtered, and evaporated to dryness. The residue was extracted with ether, and gave the *ether* as a colourless liquid (20 g.), b. p. 142°/28 mm., $n_D^{19°}$ 1·4629 (Found : C, 54·55; H, 9·1. $C_6H_{12}O_3$ requires C, 54·5; H, 9·15%). The *bisphenylurethane* crystallised from benzene–light petroleum (b. p. 40—60°) in colourless needles, m. p. 102° (Found : C, 64·9; H, 5·8; N, 7·3. $C_{20}H_{22}O_5N_2$ requires C, 64·8; H, 6·0; N, 7·6%).

(*b*) To a solution of sodium allyloxide, prepared from sodium (14 g.) and allyl alcohol (200 c.c.), was slowly added a solution of glycerol α-chlorohydrin (50 g.) in allyl alcohol (50 c.c.), and the mixture was then refluxed for 2 hours. After neutralisation with carbon dioxide and dilution with water, extraction with ether gave 40 g. of 2 : 3-dihydroxypropyl allyl ether, b. p. 140°/27 mm., which gave the same bisphenylurethane, m. p. and mixed m. p. 102°, as that described above.

2 : 3-*Diacetoxypropyl Allyl Ether.*—The previous compound (160 g.) was acetylated by being heated in acetic anhydride (700 g.) with fused sodium acetate (100 g.) at 100° for 1·5 hours. After removal of much of the solvent under reduced pressure, the residue was stirred with water (500 c.c.) for 2 hours and then extracted with chloroform. The extract, after being washed with sodium hydrogen carbonate, was evaporated to an oil which on distillation furnished the *diacetate* as a colourless liquid (236 g.), b. p. 134°/15 mm., $n_D^{17°}$ 1·4379 (Found : C, 55·25; H, 7·8. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·45%).

2 : 3-*Dibromopropyl* 2 : 3-*Diacetoxypropyl Ether.*—Bromine (180 g.) in carbon tetrachloride (200 c.c.) was added slowly during 4 hours to a solution of the diacetate (234 g.) in carbon tetrachloride (1000 c.c.), the temperature being kept at 10—12°. After being washed with sodium hydrogen carbonate, the

solvent was removed; distillation of the residue gave the *dibromide* as a colourless oil (310 g.), b. p. 170°/2 mm., $n_D^{18°}$ 1·4950 (Found: C, 31·65; H, 4·3. $C_{10}H_{16}O_5Br_2$ requires C, 31·9; H, 4·3%).

2 : 3-*Diacetoxypropyl* 2 : 3-*Bisacetylthiopropyl Ether*.—The dibromo-compound (200 g.) and potassium thiolacetate (120 g.) in ethanol (500 c.c.) were refluxed for 6 hours, then cooled, diluted with water (2000 c.c.), and extracted with ether. Removal of solvent from the dried extract and distillation of the resulting oil gave the *product* as a viscous liquid (185 g.), b. p. 169—174°/$10^{-4}$ mm., $n_D^{17°}$ 1·5035 (Found: * C, 46·6; H, 5·9; S, 16·4. $C_{14}H_{22}O_7S_2$ requires C, 45·85; H, 6·05; S, 17·5%).

*Deacetylation of* (V).—The tetra-acetate (100 g.) suspended in 25% aqueous sodium hydroxide (500 c.c.) was stirred under nitrogen at *ca.* 20° for 24 hours, and then extracted with ether to remove non-thiol material. The alkaline solution was then acidified with concentrated hydrochloric acid, the temperature being kept below 5°, and extracted with ether. Removal of the ether and distillation of the residual oil gave a pale yellow liquid (30 g.), b. p. 155°/0·02 mm., $n_D^{18°}$ 1·5390 (Found: C, 41·2; H, 7·3; S, 28·5; thiol S, 18·6; active H, 1·7. $C_6H_{14}O_3S_2$ requires C, 36·3; H, 7·1; S, 32·3; active H, 2·0%). A portion was dissolved in dry acetone (10 parts) containing 1% of hydrogen chloride, left overnight, and then neutralised with barium carbonate, evaporated, and distilled to give the *di*iso*propylidene* derivative of 2 : 3-dihydroxypropyl 2 : 3-dimercaptopropyl ether, b. p. 98°/10 mm., $n_D^{23°}$ 1·5265 (Found: C, 52·2; H, 8·3; S, 23·4. $C_{12}H_{22}O_3S_2$ requires C, 51·75; H, 8·0; S, 23·05%).

1 : 3-*Benzylidene Glycerol*.—This was prepared by the method of Hibbert and Carter (*J. Amer. Chem. Soc.*, 1929, **51**, 1601) in which glycerol and benzaldehyde are condensed in the presence of hydrogen chloride, but by maintaining a slow stream of the gas through the mixture during the course of the reaction the yield of distilled benzylidene glycerol (mixture of 1 : 2- and 1 : 3-compounds), b. p. 139—142°/0·6 mm., was raised to 65%. The solid 1 : 3-isomer was separated from the oil, and recrystallised from benzene–light petroleum (b. p. 60—80°) in small prisms (yield, 50% of the distillate). The m. p. of the product varied from 65° to 75° with different batches, presumably owing to the existence of the two forms, m. p.s 63° and 83·5°, already described in the literature (cf. Davies, Heilbron, and Jones, *J.*, 1934, 1232).

2-*Allyl Ether of* 1 : 3-*Benzylidene Glycerol*.—To a stirred suspension of 1 : 3-benzylidene glycerol (50 g.) in 50% aqueous sodium hydroxide (150 c.c.), kept at 75°, allyl bromide (72 g.) was added during 2 hours. The *product* was isolated as a colourless liquid, b. p. 136—140°/ 0·5 mm., which solidified on standing. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave needles, (22 g.) m. p. 44·5° (Found: C, 70·9; H, 7·4. $C_{13}H_{16}O_3$ requires C, 70·85; H, 7·3%).

1 : 3-*Dihydroxy*-2-*propyl Allyl Ether*.—A solution of benzylidene compound (100 g.) in ethanol (500 c.c.) and 0·2% aqueous hydrochloric acid (500 c.c.) was heated for 1 hour at 80°, and then neutralised with potassium carbonate and evaporated to a syrup. This was taken up in ether, filtered, dried, and evaporated. Distillation of the product yielded 1 : 3-*dihydroxy*-2-*propyl allyl ether* (57 g.), b. p. 134°/11 mm., $n_D^{19°}$ 1·4675 (Found: C, 54·7; H, 9·0. $C_6H_{12}O_3$ requires C, 54·5; H, 9·15%).

1 : 3-*Diacetoxy*-2-*propyl Allyl Ether*.—Acetylation of the above compound (56 g.) with acetic anhydride (250 c.c.) and sodium acetate (40 g.) gave the *diacetate* (77 g.), b. p. 135°/14 mm., $n_D^{17°}$ 1·4413 (Found: C, 55·3; H, 7·35. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·45%).

2 : 3-*Dibromopropyl* 1 : 3-*Diacetoxy*-2-*propyl Ether*.—Bromine (60 g.) in carbon tetrachloride (120 c.c.) was added during 4 hours to a solution of the above diacetate (80 g.) in carbon tetrachloride (400 c.c.), the temperature being kept below 10°. The *dibromide* distilled as a colourless liquid (115 g.), b. p. 173°/1 mm., $n_D^{18°}$ 1·4952 (Found: C, 31·7; H, 4·2. $C_{10}H_{16}O_5Br_2$ requires C, 31·9; H, 4·3%).

1 : 3-*Diacetoxy*-2-*propyl* 2 : 3-*Bisacetylthiopropyl Ether*.—The dibromo-compound (100 g.) and potassium thiolacetate (85 g.) in ethanol (750 c.c.) were refluxed for 6 hours, to yield the required *compound* as a viscous orange-coloured oil (75 g.), b. p. 175—176°/0·003 mm., $n_D^{18°}$ 1·5017 (Found: C, 46·05; H, 5·9; S, 16·8. $C_{14}H_{22}O_7S_2$ requires C, 45·85; H, 6·05; S, 17·5%).

1 : 3-*Dihydroxy*-2-*propyl* 2 : 3-*Dimercaptopropyl Ether*.—The tetra-acetate (15 g.) was hydrolysed in 25% aqueous sodium hydroxide (100 c.c.) as described for the α-analogue. Distillation of the product gave the slightly impure *dithiol* (5 g.), b. p. 150—151°/0·005 mm., $n_D^{22°}$ 1·5445 (Found: C, 37·2; H, 6·9; S, 31·0; thiol S, 30·6; active H, 1·95. $C_6H_{14}O_3S_2$ requires C, 36·3; H, 7·1; S, 32·3; active H, 2·0%). Reaction of a portion with dry acetone, containing 1% hydrogen chloride, gave the *diisopropylidene* derivative, m. p. 67° after crystallisation from methanol (Found: C, 51·6; H, 7·7; S, 22·9. $C_{12}H_{22}O_3S_2$ requires C, 51·75; H, 8·0; S, 23·05%).

*Allyloxyacetic Acid*.—To a solution of sodium allyloxide, prepared from sodium (130 g.) and allyl alcohol (1200 c.c.), was added a solution of chloroacetic acid (230 g.) in allyl alcohol (300 c.c.), at such a rate that the mixture refluxed gently (1½ hours). After refluxing for a further 2 hours, the solution was neutralised with carbon dioxide and evaporated to dryness. The residue was dissolved in water and acidified with dilute sulphuric acid, and then extracted with ether to give *allyloxyacetic acid* (204 g.), b. p. 120°/13 mm., $n_D^{22°}$ 1·4460 (Found: C, 51·8; H, 7·25; equiv., 116·9. $C_5H_8O_3$ requires C, 51·7; H, 6·95%; equiv., 116·1). A small portion, treated with bromine in carbon tetrachloride solution, gave 2 : 3-*dibromopropoxyacetic acid*, which crystallised from chloroform–light petroleum (b. p. 60—80°) in prisms, m. p. 85° (Found: C, 22·15; H, 3·0. $C_5H_8O_3Br_2$ requires C, 21·75; H, 2·9%). Esterification of allyloxyacetic acid with ethanolic sulphuric acid gave the *ethyl* ester, b. p. 177—178°, 75°/13 mm., $n_D^{14°}$ 1·4272 (Found: C, 58·6; H, 8·75. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%).

*Ethyl* 2 : 3-*Dibromopropoxyacetate*.—Treatment of a solution of ethyl allyloxyacetate (35 g.) in carbon tetrachloride (150 c.c.) with bromine (45 g.) in carbon tetrachloride (100 c.c.) gave *ethyl* 2 : 3-*dibromopropoxyacetate* (53 g.), b. p. 158—160°/15 mm., $n_D^{14°}$ 1·5060 (Found: C, 27·8; H, 4·4; Br, 52·7. $C_7H_{12}O_3Br_2$ requires C, 27·6; H, 4·0; Br, 54·6%).

*Ethyl* 2 : 3-*Bisacetylthiopropoxyacetate*.—The above dibromo-ester (20 g.) reacted with potassium

* Slight discrepancies in the analytical figures for liquid acetylated dithiols were often encountered during the course of this work. These may be due to the presence of traces of potassium acetate in the potassium thiolacetate, resulting in the formation of a small amount of the corresponding *O*-acetates, which would not be readily separable from the acetylated dithiols.

thiolacetate (30 g.) in boiling ethanol (300 c.c.) to give *ethyl* 2 : 3-*bisacetylthiopropoxyacetate* as a viscous yellow oil (17 g.), b. p. 147°/0·4 mm., $n_D^{19°}$ 1·5098 (Found : C, 44·7; H, 5·9; S, 22·1. $C_{11}H_{18}O_5S_2$ requires C, 44·85; H, 6·2; S, 21·8%).

2 : 3-*Dimercaptopropoxyacetic Acid.*—The ester (30 g.) was hydrolysed in 25% aqueous sodium hydroxide (300 c.c.) as previously described. Distillation of the product gave the *dimercapto-acid* as a colourless, viscous liquid (8 g.), b. p. 150°/0·0001 mm., $n_D^{23°}$ 1·5505 (Found : C, 33·8; H, 5·6; S, 34·1; thiol S, 34·6. $C_5H_{10}O_3S_2$ requires C, 32·95; H, 5·5; S, 35·2%).

*Ethyl* 3 : 4-*Dibromobutane*-1-*carboxylate.*—Ethyl but-3-ene-1-carboxylate (42 g.), prepared by the method of Zeidler (*loc. cit.*), in carbon tetrachloride (200 c.c.) was treated at −20° with bromine (64 g.) in carbon tetrachloride (150 c.c.), added during 2 hours. The *dibromo*-ester was obtained as a liquid (60 g.), b. p. 95—96°/0·2 mm., $n_D^{16°}$ 1·5080 (Found : Br, 55·6. $C_7H_{12}O_2Br_2$ requires Br, 55·5%).

*Ethyl* 3 : 4-*Bisacetylthiobutane*-1-*carboxylate.*—Reaction of the dibromo-ester (60 g.) with potassium thiolacetate (56 g.) in ethanol (200 c.c.) gave a yellow liquid *ester* (40 g.), b. p. 147—148°/1 mm., $n_D^{20°}$ 1·5115 (Found : C, 48·0; H, 6·7; S, 22·1. $C_{11}H_{18}O_4S_2$ requires C, 47·45; H, 6·5; S, 23·0%).

δ-*Mercapto*-γ-*valerothiolactone* (XIV).—The above ethyl ester (25 g.) was saponified, in the way previously described, with cold 30% aqueous sodium hydroxide (250 c.c.). Distillation of the product gave the *lactone* (6·8 g.), b. p. 83—84°/0·2 mm., $n_D^{17°}$ 1·5630 (Found : thiol S, 22·3. $C_5H_8OS_2$ requires thiol S, 21·6%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 138° (Found : C, 60·3; H, 5·0; N, 4·8. $C_{16}H_{15}O_2NS_2$ requires C, 60·5; H, 4·8; N, 4·4%).

A portion of the lactone was dissolved in excess of 5% aqueous sodium hydroxide, left for 1 hour at ordinary temperature, and then acidified and titrated with iodine. The thiol value (Found : 36·6%, calculated as dimercapto-acid) indicated almost complete conversion into 3 : 4-dimercaptobutane-1-carboxylic acid (Calc. for $C_5H_{10}O_2S_2$ : S, 38·6%).

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