61. *Dithiols. Part III. Derivatives of Polyhydric Alcohols.*

By R. M. Evans, (the late) J. B. Fraser, and L. N. Owen.

From butadiene monoxide, the two stereoisomeric *tetra-acetates* of 1 : 2-dimercaptobutane-3 : 4-diol have been synthesised; on deacetylation these furnish 1 : 2-*dithioerythritol* and 1 : 2-*dithiothreitol* (*di*iso*propylidene* derivatives). From pent-2-en-4-yn-1-ol, the *penta-acetate* of 1 : 2-dimercaptopentane-3 : 4 : 5-triol has been prepared. The *meso*- and the DL-form of 1 : 4-dibromo-2 : 3-diacetoxybutane have been used for the synthesis of the *tetra-acetates* of 1 : 4-dithioerythritol and 1 : 4-dithiothreitol, respectively, the free *dithiols* (*di*iso*propylidene* derivatives) being obtained on deacetylation. Similarly, tetra-acetyl mannitol 1 : 6-dibromohydrin, the preparation of which has been studied, gives the *hexa-acetate* of 1 : 6-dithiomannitol, and thence the free *dithiol*. It is necessary to use bromo-compounds for these syntheses, since the corresponding chloro-compounds do not react smoothly with potassium thiolacetate. Attempts to prepare 2 : 3-dimercaptobutane-1 : 4-diol from 2 : 3-dibromo-1 : 4-diacetoxybutane failed, owing to reduction of the dibromide to 1 : 4-diacetoxybut-2-ene by the thiolacetate. Some experiments on the deacetylation of the *triacetate* of 2 : 3-dimercaptopropanol are recorded, which indicate the occurrence of side-reactions in the process.

2 : 3-DIMERCAPTOPROPANOL (" BAL ") (I) may be considered as the parent of a series of hydroxy-dithiols in which (II) and (III) would be succeeding members. The preparation of these analogues, and of the non-vicinal compounds (IV) and (V), has now been studied, since from the pharmacological point of view the examination of such a series would be expected to provide useful information on the effect of structure both on anti-arsenical activity and also on toxicity (cf. Part II, preceding paper).

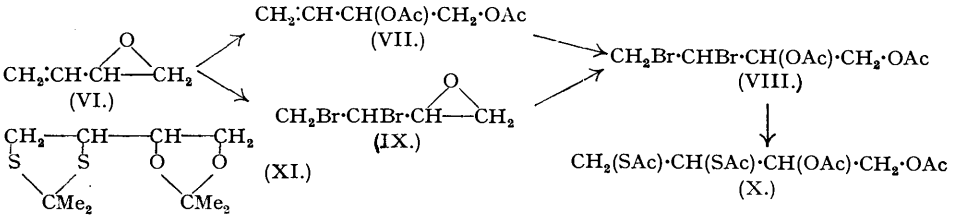
$CH_2(SH)\cdot CH(SH)\cdot CH_2\cdot OH$ (I.) $\qquad$ $CH_2(SH)\cdot CH(SH)\cdot CH(OH)\cdot CH_2\cdot OH$ (II.)

$CH_2(SH)\cdot CH(SH)\cdot CH(OH)\cdot CH(OH)\cdot CH_2\cdot OH$ (III.)

$CH_2(SH)\cdot [CH(OH)]_2\cdot CH_2\cdot SH$ (IV.) $\qquad$ $CH_2(SH)\cdot [CH(OH)]_4\cdot CH_2\cdot SH$ (V.)

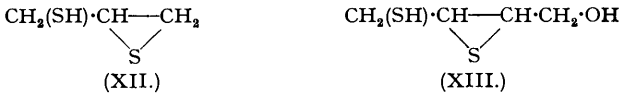
Butadiene monoxide (VI) has recently become commercially available, and is an obvious starting point for the synthesis of the dithiol (II), since it is known to undergo ready hydrolysis to butene-3 : 4-diol, which can be brominated to give 1 : 2-dibromobutane-3 : 4-diol (Cloetz, *Bull. Soc. chim.*, 1908, **3**, 418; Pariselle, *Ann. Chim. Phys.*, 1911, **24**, 403). The overall yield of dibromide by this means, however, is poor, and two other possible routes from the oxide were therefore investigated: (i) acetolysis of the oxide with acetic acid–acetic anhydride–hydrochloric

acid to give 3 : 4-diacetoxybutene (VII), followed by addition of bromine to yield 1 : 2-*dibromo*-3 : 4-*diacetoxybutane* (VIII); and (ii) addition of bromine to the oxide, to give 1 : 2-dibromo-3 : 4-epoxybutane (IX), followed by acetolysis to (VIII). The first of these alternatives proved to be the more suitable, since it gave a better yield and a purer product than the second.



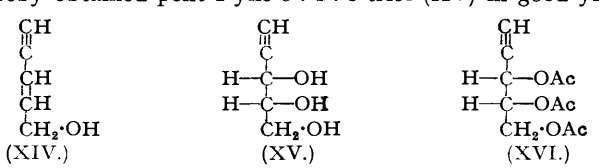
Furthermore, it was found that acetolysis with acetic anhydride–zinc chloride gave little more than half the yield obtained with acetic acid–acetic anhydride–hydrochloric acid.

Treatment of the dibromide (VIII) with potassium thiolacetate in boiling ethanol gave a product which on recrystallisation from methanol furnished 1 : 2-*diacetoxy*-3 : 4-*bisacetylthiobutane* (X). From the mother liquors a stereoisomeric *tetra-acetyl* derivative was obtained. These two isomers must correspond stereochemically to the tetrols, erythritol and threitol, but at present there is no means of allocating the particular configurations to them. The higher-melting tetra-acetyl derivative was deacetylated by being heated with ethanolic hydrogen chloride; the thiol value of the solution became constant at 75% of the theoretical, and on distillation of the product two distinct fractions were obtained. The higher-boiling material contained the required dithiol (II), since it gave a crystalline *di*iso*propylidene* derivative (XI). The lower-boiling fraction, however, consisted mainly of an anhydro-compound; it contained only one free thiol group, and gave a *bisphenylurethane*, $C_{18}H_{18}O_3N_2S_2$, indicating the possession also of one free hydroxyl group. It must have been formed, therefore, either during the deacetylation process (in which, as mentioned above, the theoretical thiol value was not attained) or in the working up of the product, by loss of one mol. of water between a thiol group and a hydroxyl group; this ready dehydration is known to occur with BAL itself, which on being heated at 110°/10 mm. gives dithioglycidol (XII) (U.S.P. 2,396,957). Several structures are possible for the anhydro-compound; from analogy with the behaviour of BAL, it may be tentatively formulated as (XIII).



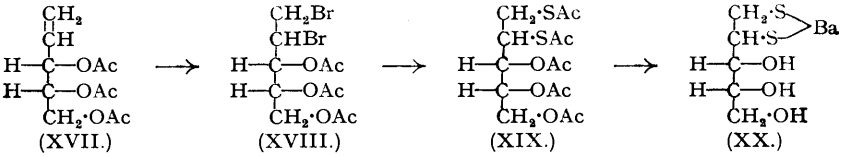
Deacetylation of the lower-melting tetra-acetyl derivative, under similar conditions, also gave a mixture of dithiol and anhydro-compound; the former was characterised as its *di*iso*propylidene* derivative, one of the stereoisomers represented by (XI).

For the preparation of the dimercaptopentanetriol (III) it was necessary to prepare 3 : 4 : 5-triacetoxypentene (XVII), a compound which had been obtained in poor yield by Lespieau (*Bull. Soc. chim.*, 1928, **43**, 657). The recent availability of pent-2-en-4-yn-1-ol (XIV) (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583), however, has led Dr. Raphael, of this College, to investigate the hydroxylation of the double bond in this compound by means of the performic acid reagent of Swern, Billen, and Scanlan (*J. Amer. Chem. Soc.*, 1946, **68**, 1505). He has thereby obtained pent-1-yne-3 : 4 : 5-triol (XV) in good yield, and has shown



that the pair of hydroxyl groups so introduced at C_3 and C_4 have the *cis*-configuration with respect to one another (private communication). Acetylation of this compound gave 3 : 4 : 5-*triacetoxypent*-1-*yne* (XVI) (a stereoisomer of the substance described by Lespieau) which underwent smooth semihydrogenation in ethyl acetate solution, when shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst, and gave an excellent yield of crystalline 3 : 4 : 5-*triacetoxypent*-1-*ene* (XVII). This was converted, with bromine in

carbon tetrachloride solution, into 1 : 2-*dibromo*-3 : 4 : 5-*triacetoxypent*-1-*ene* (XVIII), which partly crystallised, the addition of bromine evidently taking place in the two possible ways to give a mixture of two stereoisomers, differing in configuration only at position 2. Treatment of either the solid or the liquid dibromide with potassium thiolacetate gave 3 : 4 : 5-*triacetoxy*-1 : 2-*bisacetylthiopentane* (XIX) as a liquid product from which a small amount of a solid isomer was

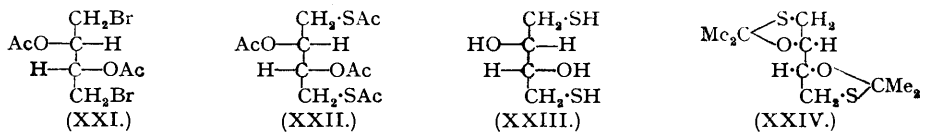


(XVII.) (XVIII.) (XIX.) (XX.)

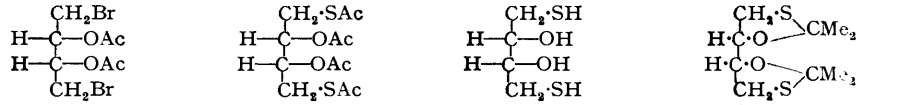
obtained. It is probable that partial Walden inversion occurs during the replacement of bromine by acetylthio-groups, so that a mixture of stereoisomeric penta-acetates is obtained, irrespective of whether the solid or the liquid dibromide is used. Trial experiments indicated that deacetylation of the penta-acetate with ethanolic hydrogen chloride, followed by distillation of the product, again resulted in partial cyclisation, and the material was therefore treated with methanolic barium methoxide, according to the method adopted in the original synthesis of " BAL-Intrav " (Danielli, Danielli, Fraser, Mitchell, Owen, and Shaw, *Biochem. J.*, 1947, **41**, 325), to yield a crude barium salt (XX) from which a solution of the free dithiol could conveniently be prepared, when required, for biological assay.

1 : 4-Dibromobutane-2 : 3-diol is known in both the *meso*- and the DL-form, corresponding respectively to the tetrols, erythritol and DL-threitol (these alcohols are frequently referred to in the literature as *meso*- or " natural " erythritol, and " *dl*-erythritol ", respectively). The isomer obtained by the oxidation of *trans*-1 : 4-dibromobut-2-ene with potassium permanganate (Thiele, *Annalen*, 1899, **308**, 337) is known to be the DL-form. The diacetate (XXI) of this reacted with potassium thiolacetate to give DL-threo-2 : 3-*diacetoxy*-1 : 4-*bisacetylthiobutane* (XXII). In contrast with the other acetylated thiols already mentioned, this compound was smoothly deacetylated by warm alcoholic hydrogen chloride to give a product which distilled without decomposition and readily crystallised. The DL-threo-1 : 4-*dimercaptobutane*-2 : 3-*diol* (DL-1 : 4-*dithiothreitol*) (XXIII) so obtained reacted with acetone to give the *di*iso*propylidene* derivative (XXIV). By a similar series of reactions, *meso*-1 : 4-dibromo-2 : 3-diacetoxybutane (XXV) (Owen, this vol., p. 241) gave meso-2 : 3-*diacetoxy*-1 : 4-*bisacetylthiobutane* (*i.e.*, *tetra-acetyl* 1 : 4-*dithioerythritol*) (XXVI), and thence 1 : 4-*dithioerythritol* (XXVII) which gave a *di*iso*propylidene* derivative (XXVIII).

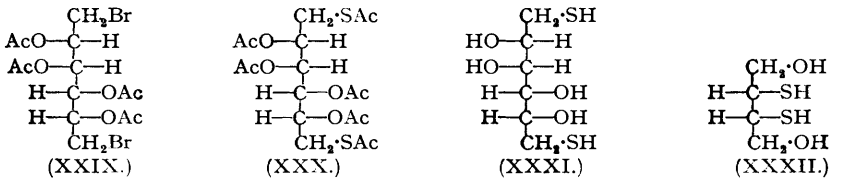
According to Vögel (*Ber.*, 1938, **71**, 1272; cf. Fischer and Armstrong, *ibid.*, 1902, **35**, 842; Perkin and Simonsen, *J.*, 1905, **87**, 862) hexa-acetyl mannitol, dissolved in acetic acid containing 50% of hydrogen bromide, is gradually converted in the course of several months into the 2 : 3 : 4 : 5-tetra-acetyl 1 : 6-dibromohydrin (XXIX), but no yield is recorded. We have found this to be only 10% after nine months, and have therefore attempted to increase both the



(XXI.) (XXII.) (XXIII.) (XXIV.)



(XXV.) (XXVI.) (XXVII.) (XXVIII.)



(XXIX.) (XXX.) (XXXI.) (XXXII.)

conversion and the rate of reaction. When the mixture was heated at 100° for two hours, the only product isolated was a small amount of monoacetyl pentabromohydrin, probably identical

with that described by Perkin and Simonsen (*loc. cit.*), but at 35° the replacement of acetoxy-groups by bromine occurred more smoothly. A 20—25% yield of the required dibromide was isolated by working up the product after the reaction had proceeded for 9 hours, and this was not improved by any further change in conditions, such as variation in hydrogen-bromide concentration. Similar treatment of hexa-acetyl sorbitol gave 2 : 3 : 4 : 5-*tetra-acetyl sorbitol* 1 : 6-*dibromohydrin*. The tetra-acetyl mannitol dibromohydrin with potassium thiolacetate yielded *hexa-acetyl* 1 : 6-*dithiomannitol* (XXX), which on deacetylation with ethanolic hydrogen chloride gave 1 : 6-*dithiomannitol* (XXXI).

An unexpected difficulty arose in the attempted preparation of 2 : 3-dimercaptobutane-1 : 4-diol (XXXII) from *meso*-2 : 3-dibromo-1 : 4-diacetoxybutane. Although the latter compound is known to react with silver acetate, to give erythritol tetra-acetate (Griner, *Bull. Soc. chim.*, 1893, **9**, 219), it behaved abnormally on treatment with potassium thiolacetate in alcohol, and was reduced to 1 : 4-diacetoxybut-2-ene, sulphur being precipitated. Similar results were also obtained when the dibromide reacted with thiolacetic acid in pyridine, or with alcoholic sodium hydrogen sulphide. The abnormal reaction is evidently associated with the secondary nature of both the vicinal halogen atoms, since, in compounds where at least one of the groups was primary, no such effect was observed. In 1905 Rosenheim and Stadler (*Ber.*, **38**, 2687) attempted to prepare αα′-dimercaptosuccinic acid by reaction of αα′-dibromosuccinic acid with sodium hydrogen sulphide, but obtained only fumaric acid, a result clearly comparable to the formation of diacetoxybut-2-ene in the reactions mentioned above.

In view of the recent availability of the four structurally isomeric dichlorobutanediols (Evans and Owen, this vol., p. 239; Owen, *ibid.*, p. 241), the reactions of their diacetates with potassium thiolacetate have been investigated. The reactivities were found to be comparatively low, and it was necessary to reflux in boiling alcohol for at least 12 hours (compared with 2—6 hours for the dibromides) to bring about complete reaction. Furthermore, under these conditions, considerable decomposition occurred, and little or none of the corresponding acetylated dithiol was obtained. A similarly unsuccessful attempt was made to prepare hexa-acetyl 1 : 6-dithio-mannitol from tetra-acetyl mannitol 1 : 6-dichlorohydrin. It is essential, therefore, to use bromo-derivatives in the reactions with potassium thiolacetate.

From the evidence now available on the dithiols described in the present series of papers it is clear that, although it is often possible to prepare the fully acetylated polyhydroxy-dithiols in a pure state, their deacetylation, except in the case of non-vicinal dithiols, frequently proceeds abnormally. In an attempt to throw some light on this reaction, the deacetylation of the *triacetate* of 2 : 3-dimercaptopropanol was investigated. When this compound was boiled under reflux with N-methanolic hydrogen chloride, the thiol content of the solution reached the theoretical value, but the product on distillation gave only a 43% yield of 2 : 3-dimercapto-propanol together with a quantity of higher-boiling material. Deacetylation of the triacetate with cold aqueous alkali resulted in the attainment of a thiol value in the solution of only 64% of the theoretical; the yield of distilled 2 : 3-dimercaptopropanol was 35%, and a considerable amount of high-boiling substance was present. 2 : 3-Dimercaptopropanol is known to undergo ready intramolecular dehydration to dithioglycidol (XII) on being heated under reduced pressure; these higher-boiling compounds probably result from intermolecular condensations. When such by-products are so readily formed from a simple monohydroxydithiol, it is not surprising that there has been a tendency for inter- or intra-molecular loss of water or hydrogen sulphide from the more complex compounds encountered in the present work. Further investigations will be necessary in order to establish the precise course of the deacetylation of these substances.

Methylation of 2 : 3-dimercaptopropanol with methyl sulphate (2 mols.) and alkali gave the *di*-S-*methyl ether* (*α-naphthylurethane*).

The absorption spectra in ethanol of a number of acetylated thiols were kindly determined by Dr. E. A. Braude, and are recorded in the table.

Compound.	$\lambda_{max.}$ A.	ϵ.
Glucothiose penta-acetate [1]	2240	7500
BAL-Intrav hexa-acetate,[2] m. p. 75—77°	2280	8800
BAL triacetate	2300	7900
1 : 2-Dimercaptobutane-3 : 4-diol tetra-acetate, m. p. 68°	2290	7900
1 : 2-Dimercaptobutane-3 : 4-diol tetra-acetate, m. p. 78°	2310	7300
threo-1 : 4-Dimercaptobutane-2 : 3-diol tetra-acetate, m. p. 73°	2290	7700
erythro-1 : 4-Dimercaptobutane-2 : 3-diol tetra-acetate, m. p. 126°	2290	7600
1 : 2-Dimercaptopentane-3 : 4 : 5-triol penta-acetate	2290	6700

[1] See Part I (*Biochem. J.*, 1947, **41**, 325).
[2] See Part II (this vol., p. 244).

The dithiols described in this and the preceding paper, and some of their fully acetylated derivatives, have been examined biologically by Dr. Miles Weatherall and Mrs. J. A. C. Weatherall, University of Edinburgh, who have found that the following compounds are approximately equal (on a mol. basis) to BAL in activity against mapharside poisoning in mice: (i) α- and (ii) β-glyceryl ethers of BAL; (iii) γ-mercaptovalerothiolactone; (iv) 1 : 2-dimercaptobutane-3 : 4-diol; (v) 1 : 2-dimercaptopentane-3 : 4 : 5-triol.

Compounds (i)—(iv) are approximately as toxic as BAL, but (v) is substantially less so. The acetates of (i), (ii), (iv), and (v) have very low toxicities, but are therapeutically ineffective. The non-vicinal dithiols behave quite differently. 1 : 4-Dithiothreitol is more toxic than BAL, and, furthermore, it greatly accelerates death when administered after mapharside; 1 : 6-dithiomannitol has a toxic action not shown by any of the other dithiols, and produces a wasting disease, accompanied by paralysis. Details of this biological work will be published elsewhere.

Experimental.

3 : 4-*Diacetoxybut*-1-*ene*.—(*a*) Butadiene monoxide (10 g.) was added slowly, with shaking, to a cooled mixture of acetic anhydride (50 g.) and concentrated hydrochloric acid (5 g.), after which the solution was heated in the steam-bath for 16 hours, and then cooled, diluted with water (300 c.c.), and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated, to yield 3 : 4-diacetoxybut-1-ene, (17 g.), b. p. 94—98°/12 mm., $n_D^{23°}$ 1·4330 (Found: Ac, 49·2. Calc. for $C_8H_{12}O_4$: Ac, 50·0%).

(*b*) Butadiene monoxide (10 g.) and acetic anhydride (50 g.), containing anhydrous zinc chloride (0·1 g.), were heated for 16 hours on the steam-bath. The yield of 3 : 4-diacetoxybut-1-ene, isolated as described above, was only 9·2 g., b. p. 94—98°/11 mm., $n_D^{23°}$ 1·4332 (Found: Ac, 47·9%).

1 : 2-*Dibromo*-3 : 4-*epoxybutane*.—Bromine (115 g.) in chloroform (250 c.c.) was added dropwise to a solution of butadiene monoxide (50 g.) in chloroform (200 c.c.) over a period of 10 hours at *ca.* 10°. The solution was then washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give 1 : 2-dibromo-3 : 4-epoxybutane (53 g.), b. p. 98—99°/10 mm., $n_D^{20°}$ 1·5435 (cf. Pariselle, *loc. cit.*).

1 : 2-*Dibromo*-3 : 4-*diacetoxybutane*.—(*a*) Bromine (95 g.) in chloroform (200 c.c.) was added gradually, during 4 hours, to a solution of 3 : 4-diacetoxybut-1-ene (100 g.) in chloroform (500 c.c.) at 10°. Evaporation of the washed and dried solution then gave 1 : 2-*dibromo*-3 : 4-*diacetoxybutane* (163 g.) as a colourless liquid, b. p. 95°/0·1 mm., $n_D^{21°}$ 1·4990 (Found: C, 29·2; H, 3·5. $C_8H_{12}O_4Br_2$ requires C, 28·95; H, 3·65%).

(*b*) The same product, but in a less pure condition, was obtained by heating a solution of 1 : 2-dibromo-3 : 4-epoxybutane (25 g.) in acetic anhydride (75 c.c.) and concentrated hydrochloric acid (7·5 c.c.) on the steam-bath for 12 hours. After working up in the usual way it distilled at b. p. 100—105°/0·2 mm., $n_D^{27°}$ 1·5260—1·5115. Yield, 23·2 g.

1 : 2-*Diacetoxy*-3 : 4-*bisacetylthiobutane*.—A solution of 1 : 2-dibromo-3 : 4-diacetoxybutane (160 g.) and potassium thiolacetate (125 g.) in ethanol (700 c.c.) was boiled under reflux, with stirring, for 6 hours. Extraction of the cooled solution, diluted with water (3000 c.c.), with chloroform gave an oil, which distilled as a dark red liquid (100 g.), b. p. 144—146°/0·01 mm., $n_D^{19°}$ 1·5096; this partly solidified on standing. The distilled material was dissolved in a small volume of warm methanol (75 c.c.) and cooled to 0°, to yield colourless needles of 1 : 2-*diacetoxy*-3 : 4-*bisacetylbutane* (31·5 g.), m. p. 78° after one further recrystallisation from methanol (Found: C, 44·7; H, 5·8; S, 19·9. $C_{12}H_{18}O_6S_2$ requires C, 44·7; H, 5·6; S, 19·9%). Light absorption: see Table. The mother liquors, on cooling to −20°, deposited a further quantity of solid material, which on recrystallisation from methanol gave a *stereoisomer* of the above tetra-acetate (11·5 g.), m. p. 68°, depressed to 55° on admixture with the isomer (Found: C, 44·9; H, 5·8; S, 19·9%). Light absorption: see Table.

1 : 2-*Dimercaptobutane*-3 : 4-*diol*.—(*a*) 1 : 2-Diacetoxy-3 : 4-bisacetylthiobutane, m. p. 78° (19·5 g.), was dissolved in N-ethanolic hydrogen chloride (100 c.c.) and kept at 60° under nitrogen for 4 hours, the thiol value of the solution then having become constant at 75% of the theoretical. The cooled solution was then neutralised with barium carbonate, filtered, evaporated, and distilled, to give two main fractions: (i) 2·5 g., b. p. 76—79°/0·05 mm., $n_D^{18°}$ 1·5800; and (ii) 2·4 g., b. p. 118—120°/0·05 mm., $n_D^{18°}$ 1·5820. The first was mainly the anhydro-compound (Found: S, 44·9. Calc.: S, 47·1%) confirmed by formation of a *bisphenylurethane*, m. p. 142° (Found: N, 7·55; S, 17·4. $C_{18}H_{18}O_3N_2S_2$ requires N, 7·5; S, 17·1%). The thiol value (Found: thiol S, 20·2%) was unchanged on treatment of the compound with cold 2N-sodium hydroxide at 20° for 24 hours. The second fraction contained the required dithiol, though not in the pure state (Found: thiol S, 32·3. Calc.: 41·6%); reaction of a portion for 24 hours with dry acetone containing 1% of anhydrous hydrogen chloride gave the *di*isopropylidene derivative, which crystallised from methanol in plates, m. p. 63° (Found: C, 51·4; H, 7·4; S, 27·4. $C_{10}H_{18}O_2S_2$ requires C, 51·2; H, 7·7; S, 27·4%).

(*b*) The lower-melting tetra-acetyl derivative (2 g.), treated similarly with boiling N-methanolic hydrogen chloride (20 c.c.) for 4 hours, gave an oil, which on distillation furnished a trace of low-boiling material (probably anhydro-compound) and a main fraction (0·6 g.) b. p. 114—116°/0·001 mm., $n_D^{20°}$ 1·5830, again consisting of a mixture of dithiol and anhydro-compound (Found: thiol S, 36·2%). On reaction with dry acetone containing a trace of sulphuric acid, it gave the *di*isopropylidene derivative of the dihydroxy-dithiol, which crystallised from methanol in plates, m. p. 82° (Found: C, 51·2; H, 7·7; S, 27·5%).

3 : 4 : 5-*Triacetoxypent*-1-*ene*.—Pent-2-en-4-yn-1-ol (65 g.) was hydroxylated with hydrogen peroxide and formic acid as described by Raphael (in the press), and the crude product, obtained by evaporation of the reaction mixture, on acetylation with acetic anhydride and sodium acetate, gave 3 : 4 : 5-*tri*-

acetoxypent-1-yne (54 g.), m. p. 51°, b. p. 120°/0·8 mm., $n_D^{18°}$ 1·4525 (Found: C, 54·6; H, 6·1. $C_{11}H_{14}O_6$ requires C, 54·5; H, 5·8%). Semihydrogenation of this compound in ethyl acetate solution in the presence of a 10% palladium–calcium carbonate catalyst gave an almost theoretical yield of 3 : 4 : 5-*triacetoxypent-1-ene*, b. p. 143°/12 mm., $n_D^{12°}$ 1·4420 (Found: C, 53·8; H, 6·3. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%) (cf. Raphael, *loc. cit.*).

1 : 2-*Dibromo*-3 : 4 : 5-*triacetoxypentane*.—A solution of bromine (37·5 g.) in carbon tetrachloride (100 c.c.) was gradually added to 3 : 4 : 5-triacetoxypent-1-ene (52 g.) in carbon tetrachloride (500 c.c.) at 10°. The product, isolated in the usual way, on distillation furnished 1 : 2-*dibromo*-3 : 4 : 5-*triacetoxypentane* (87 g.) as a colourless liquid, b. p. 125—130°/0·001 mm., which partly solidified on standing. The solid (35 g.) was separated from the liquid isomer, and crystallised from methanol in plates, m. p. 84° (Found: C, 32·8; H, 4·1. $C_{11}H_{16}O_6Br_2$ requires C, 32·7; H, 4·0%).

3 : 4 : 5-*Triacetoxy*-1 : 2-*bisacetylthiopentane*.—The solid dibromo-compound (65 g.) and potassium thiolacetate (50 g.) were dissolved in ethanol, refluxed for 6 hours, and worked up in the usual way to yield 3 : 4 : 5-*triacetoxy*-1 : 2-*bisacetylthiopentane* as a red liquid (48 g.), b. p. 150—160°/0·001 mm. (Found: S, 15·9%), from which a small amount of solid was obtained on trituration with methanol at 0°. It crystallised from this solvent in colourless needles, m. p. 92° (Found: C, 46·1; H, 5·4; S, 16·2. $C_{15}H_{22}O_8S_2$ requires C, 45·7; H, 5·6; S, 16·3%). Light absorption: see Table. The same liquid product, again depositing a small amount of the solid isomer, m. p. 92°, was also obtained by a similar reaction on the liquid dibromide.

Deacetylation of 3 : 4 : 5-*Triacetoxy*-1 : 2-*bisacetylthiopentane*.—To a stirred solution of the penta-acetate (4·2 g.) in methanol (50 c.c.), kept at −20° under nitrogen, a solution of N-methanolic barium methoxide (30 c.c.) was added, with efficient stirring, followed by dry ethanol (150 c.c.). The temperature was then allowed to rise to 10°, and, after a further ½ hour's stirring, the *barium* salt of the dithiol, which had separated as a pale yellow solid, was filtered off, rapidly washed with acetone and ether, and dried in a vacuum over phosphoric oxide. Because of the ease of oxidation shown by such barium salts in the presence of air and moisture (see Part I, *loc. cit.*) no attempt was made to purify this product, which from its analysis probably contained some co-precipitated barium acetate (Found: Ba, 47·6; S, 15·6. $C_5H_{10}O_3S_2Ba$ requires Ba, 43·0; S, 20·05%). The thiol value, however (Found: thiol S, 14·1%), was satisfactory in comparison with the total sulphur content.

DL-1 : 4-*Dibromo*-2 : 3-*diacetoxybutane*.—1 : 4-Dibromobut-2-ene, m. p. 53°, was prepared from butadiene by a modification (Owen, *loc. cit.*) of the method of Farmer, Lawrence, and Thorpe (*J.*, 1928, 737), and oxidised with neutral 5% aqueous potassium permanganate (Thiele, *loc. cit.*). This was acetylated with acetic anhydride–acetic acid–sulphuric acid to give the diacetate, m. p. 99°.

Tetra-acetyl 1 : 4-*Dithiothreitol*.—The above diacetate (40 g.) was treated with potassium thiolacetate (30 g.) in boiling ethanol. Isolation by ether extraction of the diluted solution gave an oil (32 g.), b. p. 164°/2 mm., which solidified. Recrystallisation from methanol gave large prisms (24 g.) of *tetra-acetyl* DL-1 : 4-*dithiothreitol*, m. p. 73° (Found: C, 45·0; H, 5·7; S, 19·9. $C_{12}H_{18}O_6S_2$ requires C, 44·7; H, 5·6; S, 19·9%). Light absorption: see Table.

1 : 4-*Dithiothreitol*.—A solution of the tetra-acetate (21 g.) in N-methanolic hydrogen chloride (100 c.c.) was boiled under reflux for 4 hours, and then evaporated to an oil, which on distillation furnished 1 : 4-*dithiothreitol* (9·2 g.), b. p. 125—130°/2 mm., crystallising from ether in fine needles, m. p. 42—43° (Found: C, 31·5; H, 6·75; S, 41·8; thiol S, 41·5. $C_4H_{10}O_2S_2$ requires C, 31·1; H, 6·5; S, 41·6%). The compound is readily soluble in water, alcohols, acetone, ethyl acetate, chloroform, and warm ether, and, particularly in the crude state, is somewhat hygroscopic. The *di*isopropylidene derivative was readily formed by treatment of a portion with dry acetone, containing 1% of concentrated sulphuric acid, for 24 hours at 20°. It crystallised from methanol in long needles, m. p. 78° (Found: C, 51·45; H, 7·8. $C_{10}H_{18}O_2S_2$ requires C, 51·2; H, 7·7%).

Tetra-acetyl 1 : 4-*Dithioerythritol*.—*meso*-1 : 4-Dibromo-2 : 3-diacetoxybutane (10 g.) (Owen, *loc. cit.*) and potassium thiolacetate (10 g.) in ethanol (75 c.c.) were refluxed for 2 hours. An equal volume of water was then gradually added, which dissolved the potassium bromide and precipitated a pale yellow solid, which was collected and washed with water. Purification by sublimation at 130° (bath temp.)/0·0001 mm. gave *tetra-acetyl* 1 : 4-*dithioerythritol* (7·5 g.), which crystallised from benzene or methanol in colourless plates, m. p. 126° (Found: C, 45·0; H, 5·6; S, 19·7. $C_{12}H_{18}O_6S_2$ requires C, 44·7; H, 5·6; S, 19·9%). Light absorption: see Table.

1 : 4-*Dithioerythritol*. (This preparation was kindly carried out by Mr. P. Bladon, B.Sc., A.R.C.S.)—The above tetra-acetate (6·6 g.) was boiled under reflux with N-methanolic hydrogen chloride (30 c.c.) for 5 hours in nitrogen. The solution was then evaporated under reduced pressure to a solid residue (3·2 g., 100%), which, after drying in a vacuum over potassium hydroxide, crystallised from dry ether–light petroleum (b. p. 40—60°) as a voluminous mass of small plates (2·7 g.), m. p. 80—82°, raised to 82—83° on further recrystallisation from the same solvent (Found: C, 31·4; H, 6·45; S, 40·9; thiol S, 41·1. $C_4H_{10}O_2S_2$ requires C, 31·1; H, 6·5; S, 41·6%). The *di*isopropylidene derivative, obtained in theoretical yield by the method used for the stereoisomer, crystallised from light petroleum (b. p. 40—60°) in small prisms, m. p. 145° (Found: C, 51·25; H, 7·9; S, 27·3. $C_{10}H_{18}O_2S_2$ requires C, 51·2; H, 7·7; S, 27·4%).

Action of Hydrogen Bromide on Hexa-acetyl Mannitol.—(*a*) The hexa-acetate (100 g.) was suspended in 50% hydrogen bromide in acetic acid (500 g.) and left at room temperature for 9 months, with occasional shaking. The solid tetra-acetyl 1 : 6-dibromohydrin was then collected and dried in a vacuum over potassium hydroxide. It crystallised from acetic acid in large prisms (10 g.), m. p. 199° (Found: Br, 33·6. Calc. for $C_{14}H_{20}O_8Br_2$: Br, 33·6%).

(*b*) The hexa-acetate (5 g.) in the same reagent (30 c.c.) was heated at 100° for 2 hours. The solid (0·1 g.), which separated on cooling, crystallised from ethanol in prisms, m. p. 138° (Found: Br, 74·3. Calc. for $C_8H_{11}O_2Br_5$: Br, 74·2%).

(*c*) The hexa-acetate (5 g.) in 30% hydrogen bromide in acetic acid (25 c.c.) was heated at 35°, samples being removed at intervals, precipitated with water, taken up in chloroform, washed with sodium hydrogen carbonate solution, evaporated to constant weight at 80°/20 mm., and analysed for

bromine content, with the following results: 19·9 (1 hour); 29·8 (2 hours); 36·8 (4 hours); 41·6 (8 hours) (Calc. for $C_{14}H_{20}O_8Br_2$: Br, 33·6%).

(*d*) The hexa-acetate (150 g.) was suspended in 25% hydrogen bromide in acetic acid (700 g.) and kept at 35° for 9 hours. The 1 : 6-dibromide (25 g.) was collected and recrystallised from acetic acid in prisms, m. p. 200°.

Action of Hydrogen Bromide on Hexa-acetyl Sorbitol.—The hexa-acetate (0·5 g.), on treatment with 25% hydrogen bromide in acetic acid (3 c.c.) for 6 hours at 37° gave 2 : 3 : 4 : 5-*tetra-acetyl sorbitol* 1 : 6-*dibromohydrin* (0·15 g.), which crystallised from acetic acid in prisms, m. p. 196° (Found: C, 35·4; H, 4·3. $C_{14}H_{20}O_8Br_2$ requires C, 35·8; H, 4·3%).

Hexa-acetyl 1 : 6-*Dithiomannitol.*—A suspension of the tetra-acetyl mannitol dibromohydrin (24 g.) in ethanol (150 c.c.) containing potassium thiolacetate (15 g.) was boiled under reflux for 7 hours. After dilution with water the solid *hexa-acetyl* 1 : 6-*dithiomannitol* (22 g.) was collected and recrystallised from acetic acid in plates, m. p. 188° (Found: C, 46·2; H, 5·6; S, 13·3. $C_{18}H_{26}O_{10}S_2$ requires C, 46·3; H, 5·6; S, 13·7%). It was almost insoluble in water, alcohol, and ether; moderately soluble in chloroform, hot dioxan, and hot acetic acid.

1 : 6-*Dithiomannitol.*—The hexa-acetyl dithiol (20 g.) was boiled under reflux with N-methanolic hydrogen chloride (200 c.c.) for 6 hours under nitrogen and then evaporated to dryness. Recrystallisation of the residue from water (30 c.c.) gave a product (6·5 g.), m. p. *ca.* 166°, showing 87% of the theoretical thiol value. Several recrystallisations from water or dioxan gave colourless needles of 1 : 6-*dithiomannitol*, m. p. 172° (Found: C, 34·0; H, 6·5; S, 29·5; thiol S, 29·8. $C_6H_{14}O_4S_2$ requires C, 33·6; H, 6·6; S, 29·9%). The compound is surprisingly sparingly soluble in cold water, and, though soluble in dilute aqueous alkali, is reprecipitated on acidification, except when the neutralisation is effected by boric acid. The enhanced solubility in the presence of borates is not unexpected, in view of the known tendency of polyhydric alcohols to undergo complex-formation with boric acid.

Reactions of DL-2 : 3-*Dibromo*-1 : 4-*diacetoxybutane.*—(*a*) The dibromide, m. p. 87° (145 g.), and potassium thiolacetate (112 g.) were boiled under reflux in ethanol (500 c.c.) for 4 hours. The solution, which had become very dark, was then diluted with water (2000 c.c.), filtered to remove the precipitated sulphur, and extracted with ether. Distillation of the product gave a main sulphur-free fraction (52 g.), b. p. 130°/18 mm., $n_D^{21°}$ 1·4498, consisting of 1 : 4-diacetoxybut-2-ene, characterised by reaction of a portion with bromine in carbon tetrachloride solution to give the original dibromide, m. p. and mixed m. p. 87°.

(*b*) A solution of the dibromide (4 g.) and thiolacetic acid (2·5 g.) in dry pyridine (25 c.c.) was kept at room temperature for 48 hours. Most of the pyridine was then removed under reduced pressure, and the residue was taken up in ether, washed with dilute sulphuric acid, and with water, dried (Na_2SO_4), and evaporated to a semi-solid residue. The solid material consisted of a mixture of unchanged dibromide and sulphur; the liquid portion was 1 : 4-diacetoxybut-2-ene, b. p. 124°/17 mm., $n_D^{20°}$ 1·4500.

(*c*) The dibromide (7 g.) was dissolved in 7% methanolic sodium hydrogen sulphide (70 c.c.) and kept for 5 days at 18—20°. On acidification, sulphur was precipitated, and extraction of the filtrate yielded only 1 : 4-diacetoxybut-2-ene, b. p. 125°/17 mm., $n_D^{20°}$ 1·4502.

Reactions of the Dichloro-compounds with Potassium Thiolacetate.—These were carried out under the same conditions as for the corresponding dibromides, except that a longer time of heating was necessary, preliminary experiments having shown that much unchanged material was recovered if the reaction was stopped after 2—3 hours. The reaction mixtures, which became very dark, were worked up in the usual way.

(*a*) No identifiable products were obtained from 1 : 3-dichloro-2 : 4-diacetoxybutane, 2 : 3-dichloro-1 : 4-diacetoxybutane, or tetra-acetyl mannitol 1 : 6-dichlorohydrin.

(*b*) 1 : 2-Dichloro-3 : 4-diacetoxybutane (5 g.) and potassium thiolacetate (5 g.), refluxed in ethanol (50 c.c.) for 16 hours, gave a semi-solid product (0·6 g.), b. p. 120—150°/0·001 mm., which on crystallisation from methanol gave 0·15 g. of the higher-melting stereoisomer of 1 : 2-dimercaptobutane-3 : 4-diol tetra-acetate, m. p. and mixed m. p. 78°.

(*c*) *erythro*-1 : 4-Dichloro-2 : 3-diacetoxybutane (Owen, *loc. cit.*) (7 g.) and potassium thiolacetate (7 g.) were refluxed in ethanol (100 c.c.) for 14 hours. The semi-solid product (0·8 g.) gave 0·2 g. of 1 : 4-dithioerythritol tetra-acetate, m. p. and mixed m. p. 126°, after crystallisation from methanol.

(*d*) *threo*-1 : 4-Dichloro-2 : 3-diacetoxybutane (3 g.) and potassium thiolacetate (3 g.) in ethanol (40 c.c.) were refluxed for 12 hours. The product distilled at *ca.* 120°/0·0001 mm. as an oil (0·7 g.) which deposited 0·05 g. of 1 : 4-dithiothreitol tetra-acetate, m. p. and mixed m. p. 73° after crystallisation from methanol.

3-*Acetoxy*-1 : 2-*bisacetylthiopropane* (*Triacetyl BAL*).—Acetylation of BAL (50 g.) with acetic anhydride (250 g.) and fused sodium acetate (60 g.) gave the *triacetate* (98 g.), b. p. 139°/0·1 mm., $n_D^{20°}$ 1·5140 (Found: C, 43·4; H, 5·5. $C_9H_{14}O_4S_2$ requires C, 43·2; H, 5·6%). Light absorption: see Table.

Hydrolysis of Triacetyl BAL.—(*a*) The triacetate (20 g.) was heated under reflux in N-methanolic hydrogen chloride (100 c.c.) for 3 hours; the thiol content of the solution had then become constant at the calculated value. The cooled solution was neutralised with barium carbonate, filtered, and evaporated, and the product was distilled to give a main fraction (4·3 g.), b. p. 105—107°/7 mm., $n_D^{18°}$ 1·5730, consisting essentially of BAL (purity by iodine titration, 94%). A higher-boiling residue (2 g.) was not further examined.

(*b*) The triacetate (16 g.) was stirred with 20% aqueous sodium hydroxide (100 c.c.) at 20° under nitrogen. After 48 hours, the thiol value of the solution became constant at 64% of the theoretical. After 72 hours, the solution was acidified with hydrochloric acid and continuously extracted with ether for 24 hours. Removal of ether from the dried extract and distillation of the product gave a main fraction (2·8 g.), b. p. 100°/8 mm., $n_D^{15°}$ 1·5730, consisting of BAL (purity, by iodine titration, 97%), and a second fraction (1·4 g.), b. p. 160—170°/0·001 mm., $n_D^{15°}$ 1·6070 (Found: thiol S, 32·0%); the residue in the distillation flask amounted to 2·3 g.

2 : 3-*Bismethylthiopropanol.*—Methyl sulphate (40 g.) was added dropwise to a vigorously stirred

solution of BAL (20 g.) in 20% aqueous sodium hydroxide (100 c.c.), at 75—95° under nitrogen, during 1 hour. Extraction of the cooled solution with ether and fractionation of the product gave the *di*-S-*methyl ether* as a colourless oil (18 g.), b. p. 127—130°/9 mm., $n_D^{19°}$ 1·5488, which gave no thiol reaction (Found : C, 39·7; H, 8·0. $C_5H_{12}OS_2$ requires C, 39·4; H, 7·95%). The *α-naphthylurethane* crystallised from light petroleum in needles, m. p. 71° (Found : C, 59·7; H, 6·0. $C_{16}H_{19}O_2S_2N$ requires C, 59·75; H, 5·95%).

The authors are indebted to Sir Ian Heilbron, D.S.O., F.R.S., for his continued interest, and to the Medical Research Council for a grant.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, April 29th,* 1948.]