Dithiols. Part XVI. The O-β-D-Glucoside of 1 : 3-Dimercaptopropan-2-ol.*

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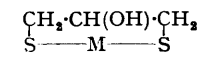
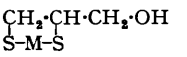
The hexa-acetyl derivative of the above glucoside has been synthesised from 1 : 3-dihydroxyprop-2-yl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside, which is conveniently prepared by selective acid hydrolysis of its *O*-benzylidene compound. Deacetylation of the hexa-acetyl derivative gives the dithiol (isolated as the barium salt); an anhydro-compound has also been obtained.

ALTHOUGH 1 : 3-dimercaptopropan-2-ol is more toxic than 2 : 3-dimercaptopropanol (BAL), it is reported to be more effective than the latter in reversal of succinoxidase inhibition caused by cadmium, mercury, and bismuth poisoning (Barron and Kalnitsky, *Biochem. J.*, 1947, **41**, 346); possibly the six-membered metal-containing ring (I) is more stable for those elements than the five-membered structure (II) derived from BAL. The toxicity of BAL is considerably reduced when it is administered in the form of its *O*-glucoside (Danielli, Danielli, Mitchell, Fraser, Owen, and Shaw, *ibid.*, p. 325), and the same would be expected to apply to the analogous derivative of 1 : 3-dimercaptopropan-2-ol.



(I)



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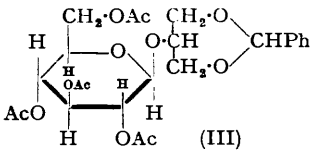

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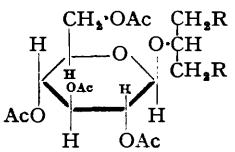
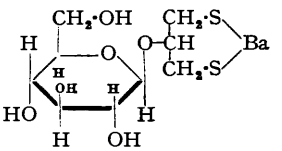
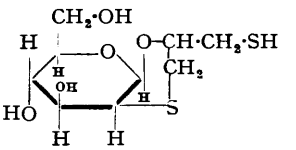


(IV; R = OH) * (VI; R = SAc)
(V; R = O·SO$_2$·C$_6$H$_4$Me-*p*)



(VII)



(VIII)

Formation of the glucoside by reaction of the 1 : 3-dithiol with glucose or with acetobromoglucose is not feasible because reaction would occur preferentially with the thiol rather than the hydroxy-group. A synthesis must therefore involve either protection of the dithiol (*e.g.*, as the *SS'*-benzylidene derivative) before reaction with the sugar, or the introduction of the thiol groups after the *O*-glucosidic linkage has been formed. The latter approach appeared the more promising and an attempt was made to convert 1 : 3-dibromopropan-2-ol into its glucoside, with the object of eventual replacement of halogen by thiol. However, reaction of the dibromohydrin with acetobromoglucose in the presence of silver carbonate gave a bromine-free product, and investigation showed that the dibromohydrin itself was rapidly debrominated by silver carbonate alone. A less direct method was therefore necessary.

Carter (*Ber.*, 1930, **63**, 1684) has described the small-scale preparation of 1 : 3-dihydroxyprop-2-yl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (IV) by catalytic hydrogenation of the 1 : 3-benzylidene compound (III), obtained by condensation of acetobromoglucose with 1 : 3-*O*-benzylideneglycerol. The preparation of the benzylideneglycerol is tedious, because of the low yield of the 1 : 3-isomer which has to be separated from the considerable proportion of 1 : 2-compound also formed (cf. Evans and Owen, *J.*, 1949, 244; and references there cited), but it has now been found (by development of some preliminary observations by Mr. M. E. Baguley of this Department) that perchloric acid is an effective catalyst not

* Part XV, preceding paper.

only for the initial condensation of benzaldehyde with glycerol but also for the partial isomerisation of the unwanted 1 : 2- into the 1 : 3-compound; a 40% yield of recrystallised 1 : 3-*O*-benzylideneglycerol was thus obtained. Conversion into the 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside proceeded smoothly, but removal of the benzylidene group by Carter's method was impracticable on a large scale owing to the considerable quantity of catalyst required (Carter used palladium black in amount almost equal to that of the benzylidene compound). Pilot experiments showed that the benzylidene group was considerably more sensitive towards acid hydrolysis than either the glycosidic linkage or the acetyl groups, and conditions were devised under which 10—20-g. quantities of the glucoside (IV) could be prepared in *ca.* 80% yield by controlled hydrolysis in aqueous-alcoholic sulphuric acid. Introduction of the thiol groups followed Chapman and Owen's general method (*J.*, 1950, 579), (IV) being converted into its crystalline ditoluene-*p*-sulphonate (V), which with potassium thiolacetate gave the pure hexa-acetyl derivative (VI) of the glucoside.

Deacetylation with methanolic barium methoxide, as previously carried out on many acetylated polyhydroxy-dithiols, was not applicable in the present instance because of the low solubility of the hexa-acetate (VI) in the reagent, but when the compound was treated with ethanolic sodium ethoxide it rapidly dissolved, and the thiol value of the solution attained over 90% of the theoretical value, indicating that deacetylation had largely followed a normal course, and was accompanied by only a small amount of cyclisation or other side-reactions. Addition of methanolic barium methoxide then precipitated the dithiol as a barium salt (VII). Although the latter was not pure, its quality was similar to that of many preparations of the isomeric derivative of BAL; the ratio of thiol to total sulphur was 0·81 (cf. preceding paper).

Attempts to isolate the free dithiol were no more successful than the earlier experiments on BAL-glucoside (Danielli *et al.*, *loc. cit.*; and unpublished observations). Removal of sodium as sodium chloride, from the solution obtained by deacetylation with ethanolic sodium ethoxide, gave on evaporation a product which contained only one free thiol group; analysis and light-absorption properties (which failed to indicate the presence of a disulphide) indicated that it was probably an anhydro-derivative, such as (VIII). This behaviour is typical of glucosides and hexitol ethers of dimercapto-propanol and -butanol; although they can be obtained in solution, all attempts at isolation have resulted in loss of thiol value, and storage as the barium salt still remains the most satisfactory procedure. The only instance in which the pure dithiol has been isolated from its barium salt was with the tetramethyl ether of BAL-glucoside (Miles and Owen, *J.*, 1950, 2934), in which cyclisation cannot occur.

Experimental

1 : 3-O-*Benzylideneglycerol.*—A mixture of benzaldehyde (253 g.), glycerol (216 g.), and 60% perchloric acid (2·5 c.c.), heated (water-bath at 80—90°) in a stream of nitrogen, at 60—70 mm., became clear in 40 min., and after a further 10 min. it was cooled, diluted with ether (400 c.c.), and washed with 1% aqueous potassium carbonate (2 × 500 c.c.). The dried (K_2CO_3) ethereal solution was evaporated to an oil (325 g.) which was dissolved in warm benzene (300 c.c.), diluted with petroleum (400 c.c.; b. p. 80—100°), decanted from a small amount of oil, and cooled to −10° to give the 1 : 3-benzylidene derivative (67 g.), m. p. 64—68°. Dilution of the mother-liquors with more petroleum gave a heavy oil, which was removed and mixed with perchloric acid (0·5 c.c.); this partly crystallised at 0°, and filtration afforded a further 82 g. of crude 1 : 3-benzylidene derivative, m. p. 47—55°. By re-treatment of the oily filtrate with more perchloric acid the total yield of crude solid derivatives was raised to 180 g. Recrystallisation from benzene–light petroleum (3 : 4) gave 74 g., m. p. 65—67°, and 65 g., m. p. 60—65° (the mixture of stereoisomers usually obtained has a m. p. in the range 60—70°).

During recrystallisation of the crude material the temperature should not be above 50°, and the warm solution should be chilled rapidly; otherwise, the presence of traces of perchloric acid catalyses the re-establishment of the 1 : 2 $\rightleftharpoons$ 1 : 3 equilibrium, with consequent heavy loss of the 1 : 3-isomer.

2-O-(2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucosyl*)*glycerol.*—A suspension of 1 : 3-*O*-benzylidene-2-*O*-(2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucosyl)glycerol (29 g.) (Carter, *Ber.*, 1930, **63**, 1684) in

ethanol (120 c.c.) at 50° was vigorously stirred during the rapid addition of N-sulphuric acid (120 c.c.) (preheated to 50°) and for a further 7 min. (the mixture became homogeneous in 2 min.). The solution was then quickly cooled to 0° (3 min.) and maintained at 0° whilst being neutralised with barium carbonate (40 min.). Barium salts were then filtered off and washed with hot ethanol, and the filtrate and washings were evaporated to a syrup, which was dried by azeotropic evaporation with benzene–ethanol. It was then dissolved in hot benzene (50 c.c.), filtered, and diluted with ether (25 c.c.); the cooled solution deposited a solid (17·5 g.) which on recrystallisation from benzene–ether gave the 2-*O*-(tetra-acetyl-β-glucosyl)glycerol as needles, m. p. 101—102°, $[\alpha]_D^{20}$ −22° (*c*, 5 in H_2O). Carter (*loc. cit.*) gives m. p. 103° (corr.), $[\alpha]_D^{19}$ −22·1° (in H_2O).

Ditoluene-p-*sulphonate*. A solution of the above compound (14 g.) with toluene-*p*-sulphonyl chloride (12·5 g.) in pyridine (140 c.c.) was kept at 0° overnight. Water (5 c.c.) was then added, and most of the pyridine was removed under reduced pressure. The residue was worked up with chloroform in the usual way and gave an oil, which was dissolved in hot methanol (40 c.c.) and light petroleum (b. p. 60—80°) (10 c.c.); after storage in the refrigerator the *derivative* (17·5 g.) crystallised. Recrystallisation from methanol gave prisms, m. p. 107—109°, $[\alpha]_D^{20}$ +1·5° (*c*, 4 in $CHCl_3$) (Found: C, 50·7; H, 5·4; S, 8·7. $C_{31}H_{38}O_{16}S_2$ requires C, 50·9; H, 5·2; S, 8·8%).

1 : 3-*Bisacetylthioprop*-2-*yl* 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside*.—A solution of the ditoluene-*p*-sulphonate (12 g.) and potassium thiolacetate (4·7 g.) in ethanol (150 c.c.) was stirred and boiled for an hour under reflux in a slow stream of nitrogen. The precipitated potassium toluene-*p*-sulphonate was filtered off and washed with hot ethanol, and the filtrate and washings were evaporated under reduced pressure. The residue was treated with water and chloroform, and the organic layer was dried and evaporated to give a gelatinous solid, which was dissolved in hot ethanol (50 c.c.) and diluted with light petroleum (100 c.c.). The solution was cooled slowly, with constant stirring, to −20°, and the gelatinous precipitate was collected and washed with ethanol–light petroleum (1 : 3); it retained a considerable amount of solvent which was removed at 10^{-4} mm. to give the *bisthiolacetate* as a microcrystalline solid, m. p. 98—102°, $[\alpha]_D^{19}$ +13·3° (*c*, 6 in $CHCl_3$) (Found: C, 47·0; H, 5·6; S, 11·7; Ac, 48·4. $C_{21}H_{30}O_{12}S_2$ requires C, 46·8; H, 5·6; S, 11·9; Ac, 48·0%). Light absorption in ethanol: max. 2280 Å (ε 8300).

Deacetylation. Quantitative tests showed that when the above compound was treated, under nitrogen, with excess of methanolic sodium methoxide at 20°, over 90% of the theoretical thiol value was attained in 30 min., as estimated by acidification and titration with iodine. The following preparative experiments were carried out:

(i) The hexa-acetyl compound (1·1 g.) was stirred at 0°, under nitrogen, with 0·3N-methanolic sodium methoxide (20 c.c.). When the mixture became homogeneous (30 min.), 1·2N-methanolic barium methoxide (5 c.c.) was added. The clear solution was warmed to 35°, the barium salt of the dithiol being suddenly precipitated. It was collected by centrifugation, and washed successively with dry methanol, dry ethanol, dry ether, and then dried in a vacuum over phosphoric oxide; it formed a fine white powder (0·8 g.) (Found: C, 22·2; H, 4·2; S, 11·8; thiol-S, 9·6; Ba, 39·2. Calc. for $C_9H_{16}O_6S_2Ba$: C, 25·6; H, 3·8; S, 15·2; Ba, 32·6%). The analysis indicated that it contained other adsorbed barium salts, but the thiol-S/total-S ratio, 0·81, was satisfactory.

(ii) The hexa-acetyl compound (1·9 g.) was shaken at 0° under nitrogen with ethanolic sodium ethoxide, from sodium (0·3 g.) and ethanol (20 c.c.). The solution (the thiol value of which had attained 91% of the theoretical for complete deacetylation) was then treated with 99% of the theoretical quantity (based on total sodium) of ethanolic hydrogen chloride, and the precipitated sodium chloride was filtered off. The filtrate was evaporated to a syrup which was dissolved in dioxan (15 c.c.), filtered, and freeze-dried in a high vacuum, to give a very hygroscopic, colourless glass (0·95 g.), probably the *anhydro*-derivative of the dimercaptopropyl-glucoside (Found: C, 40·0; H, 6·65; thiol-S, 12·8. $C_9H_{16}O_5S_2$ requires C, 40·3; H, 6·0; thiol-S, 12·0%). Light absorption in ethanol: infl. *ca.* 2250 Å (ε 400). Although initially readily soluble in ethanol, it became insoluble after storage for a few weeks.

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