Dithiols. Part XXIV.[1] Proof of the Epoxide Chirality in 2,3-Epoxypropyl β-D-Glucopyranoside by Correlation with (*R*)-2,3-Thiocarbonyldithiopropanol

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Epoxidation of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside is stereoselective and gives a 7 : 3 preponderance of the (*R*)-epoxide; this is proved by conversion into the (*R*)-trithiocarbonate, followed by hydrolysis to give (*R*)-2,3-(thiocarbonyldithio)propan-1-ol. Epoxidation of the α-anomer is only slightly stereoselective. Conversion of the glycosidic trithiocarbonate into the dithiocarbonate (carbonyl form), followed by solvolysis, provides a new synthesis of 2,3-dimercaptopropyl glucopyranoside.

2,3-EPOXYPROPYL β-D-GLUCOPYRANOSIDE (2) has been studied recently as an enzyme inhibitor.[2,3] Prepared by epoxidation of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, followed by deacetylation, the compound has a new chiral centre, but the steric course of the epoxidation has not been clarified. During investigations on the reactions of sugar epoxides with sulphur nucleophiles we had independently synthesised the tetra-acetate (1), and have now completed a simple sequence of reactions which determines the absolute configuration of the epoxide. The method, with obvious modifications, could also be applied to the epoxypropyl sugar ethers prepared by Bessell and Westwood.[3]

The tetra-acetate (1), as isolated in bulk from the

[1] Part XXIII, A. K. M. Anisuzzaman and L. N. Owen, *J. Chem. Soc.* (*C*), 1967, 1021.

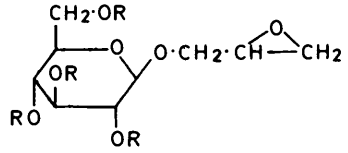
[2] J. E. G. Barnett and A. Ralph, *Carbohydrate Res.*, 1971, **17**, 231.

[3] E. M. Bessell and J. H. Westwood, *Carbohydrate Res.*, 1972, **25**, 11.

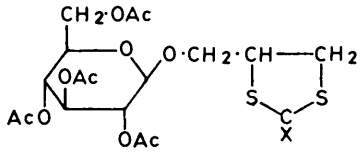
epoxidation reaction, had a wide melting range and was clearly a mixture of diastereoisomers. Partial separation was effected by a combination of t.l.c. and crystallisation to give two fractions: (i) m.p. 118—125°. $[\alpha]_D$ −23·0°, and (ii) m.p. 105—113°, $[\alpha]_D$ −16·0°. Reaction of the former with potassium *O*-methyl dithiocarbonate in methanol gave a trithiocarbonate (3), which on acidic hydrolysis furnished 2,3-(thiocarbonyldithio)propan-1-ol (5), $[\alpha]_D$ +265°, the *R*-enantiomer of which is reported [1] to show $[\alpha]_D$ +291°. Consequently the glycosidic trithiocarbonate (3) must have existed to the extent of about 95% in the *R*-configuration (6). Because conversion of a terminal epoxide, *via* an intermediate episulphide, into a trithiocarbonate occurs with inversion of configuration,[4] fraction (i) of the epoxypropyl compound must have consisted almost entirely of the diastereoisomer with configuration (7), which also is *R*.

diastereoisomers was therefore not achieved, but conversion of the oil into the trithiocarbonate [the α-analogue of (3)], followed by acidic hydrolysis, gave 2,3-(thiocarbonyldithio)propan-1-ol (5), $[\alpha]_D$ +6·1°, containing therefore only a very slight preponderance of the *R*-form. Thus, in contrast to the β-glucoside, epoxidation of allyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside occurs with insignificant stereoselectivity [*R* : *S* ratio 51 : 49]. Inspection of models does not reveal any obvious reason for this difference, the conformational mobility of the allyl group making it impossible to assess any hindrance to attack on one side of the double bond.

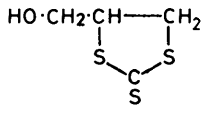
During early attempts to improve the pharmacological properties of 2,3-dimercaptopropanol (British Anti-Lewisite; 'BAL') the acetylated glucoside (8) was prepared by reaction of 2,3-dibromopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside with potassium thioacetate,[5,6]



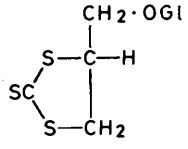
(1) R = Ac
(2) R = H



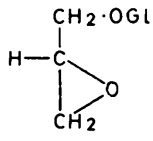
(3) X = S
(4) X = O



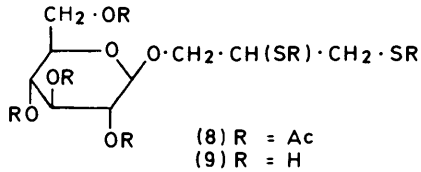
(5)



(6)



(7)



(8) R = Ac
(9) R = H

Gl = tetra-*O*-acetylglucosyl

Treatment of fraction (ii) in a similar way gave a trithiocarbonate from which the 2,3-(thiocarbonyldithio)propan-1-ol (5), obtained by hydrolysis, had $[\alpha]_D$ +25·5°. Fraction (ii) thus contained only a small preponderance of the *R*- over the *S*-form (54 : 46). Extrapolation shows that the pure (*R*)- and (*S*)-epoxides (1) would have $[\alpha]_D$ −24° and −7°, respectively.

When an unfractionated sample of the epoxide was subjected to the same sequence, the trithiocarbonate (5) so obtained had $[\alpha]_D$ +108·5°, indicating a 7 : 3 mixture of the *R*- and the *S*-form. Epoxidation of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside is thus markedly stereoselective. Calculation of the *R* : *S* ratio from the rotation of the crude epoxide was not justifiable, because some impurity was present (t.l.c.); purification was avoided because it might have affected the ratio.

We then prepared 2,3-epoxypropyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside, but, like Bessell and Westwood,[3] could not induce it to crystallise. Separation of the

but deacetylation failed to give the pure glucoside (9). The availability of the trithiocarbonate (3) offered a possible alternative route, but although reduction with lithium aluminium hydride [7] should in principle give the glucoside (9) the probability of the formation of insoluble intermediate complexes made it doubtful whether complete reduction could be easily effected. Hydrolysis under basic conditions was also discounted because trithiocarbonates are cleaved only by drastic treatment. The derivative (3) was therefore treated with mercury(II) acetate, which converted it into the dithiocarbonate (4), expected to be more amenable to basic hydrolysis; [8] indeed subsequent reaction with sodium methoxide in methanol afforded the glucoside (9). This could not be crystallised, but on acetylation it afforded the crystalline hexa-acetyl compound (8) in good yield. The crystalline α-analogue of the latter compound was obtained by a similar series of reactions on the α-analogue of the trithiocarbonate (3).

[4] A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1960, 1024.
[5] J. F. Danielli, M. Danielli, J. B. Fraser, P. D. Mitchell, L. N. Owen, and G. Shaw, *Biochem. J.*, 1947, **41**, 325.
[6] R. M. Evans and L. N. Owen, *J. Chem. Soc.*, 1949, 244.
[7] S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1960, 1030.
[8] J. K. M. Sanders and L. N. Owen, unpublished observations.

EXPERIMENTAL

Unless otherwise specified, i.r. spectra were measured for solutions in chloroform, ^1H n.m.r. spectra for solutions in deuteriochloroform (Varian A60 instrument), and optical rotations for solutions in chloroform (Perkin-Elmer 141 polarimeter). Organic extracts were dried over magnesium sulphate. The adsorbent for t.l.c. was Kieselgel GF_{254} (Merck); that for column chromatography was silica gel MFC (Hopkin and Williams). Petroleum refers to the fraction of b.p. 40—60°.

2,3-*Epoxypropyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucoside* (1).—(*a*) Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside [9] (10 g) was added to 0·5M-perbenzoic acid in chloroform (70 ml), and the solution was set aside for 70 h. It was then washed with aqueous sodium carbonate and with water, dried, and evaporated. The solid residue was recrystallised from chloroform–petroleum to give the epoxide (7·5 g), m.p. 100—119°, $[\alpha]_D^{21}$ −19·8° (Found: C, 50·7; H, 5·9. Calc. for $C_{17}H_{24}O_{11}$: C, 50·5; H, 6·0%) (lit.,[2] m.p. 115—117°, $[\alpha]_D^{30}$ −18·9°; lit.,[3] m.p. 105—106°, $[\alpha]_D^{30}$ −19°).

(*b*) A similar preparation of the epoxide gave a product which was partly separated by column chromatography (ether) followed by recrystallisation from chloroform–petroleum into two fractions showing maximum and minimum rotation: (i) m.p. 118—125°, $[\alpha]_D^{25}$ −23·0° (*c* 0·4), and (ii) m.p. 105—113°, $[\alpha]_D^{25}$ −16·0° (*c* 0·7).

2,3-(*Thiocarbonyldithio*)*propyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucoside* (3).—2,3-Epoxypropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside [preparation (*a*)] (295 mg) was added to a mixture of potassium hydroxide (382 mg) and carbon disulphide (1·5 ml) in dry methanol (10 ml). The solution was set aside for 24 h, and was then poured into water and extracted with ether to give a solid, which after purification by t.l.c. (chloroform) and recrystallisation from ether–petroleum gave the yellow *trithiocarbonate* (86 mg), m.p. 123—132°, $\nu_{max.}$ 1750 cm^{-1}, τ 4·7—6·5 (12H, m) and 7·89, 7·92, 7·96, and 7·99 (12H, 4s, 4 OAc) (Found: C, 43·5; H, 4·9; S, 19·1. $C_{18}H_{24}O_{10}S_3$ requires C, 43·5; H, 4·9; S, 19·4%).

2,3-(*Thiocarbonyldithio*)*propan*-1-*ol* (5) *from* 2,3-*Epoxypropyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucoside*.—(*a*) The epoxide of $[\alpha]_D$ −23° (346 mg) was added to a mixture of potassium hydroxide (435 mg) and carbon disulphide (3 ml) in dry methanol (11 ml), and the solution was boiled under reflux for 3 h to afford the trithiocarbonate (3) (108 mg), m.p. 126—132°, $[\alpha]_D^{23}$ +84·2° (*c* 0·65), isolated as described above. This glucoside (75 mg) was boiled under reflux for 2 h with 4N-hydrochloric acid (75 ml), and the cooled solution was extracted with chloroform to give an oil, which by t.l.c. (chloroform) furnished 2,3-(thiocarbonyldithio)propan-1-ol (19 mg), $[\alpha]_D^{23}$ +265° (*c* 0·6), $\nu_{max.}$ 1085 and 3375 cm^{-1} (lit.,[1] $[\alpha]_D$ +291° for *R*-compound). The i.r. spectrum was identical with that of an authentic sample.

(*b*) The epoxide of $[\alpha]_D$ −16° (306 mg) under similar conditions gave the trithiocarbonate (3) (109 mg), m.p. 95—110°, $[\alpha]_D^{23}$ +49·1° (*c* 1·0), a portion (72 mg) of which, on hydrolysis in the same way gave 2,3-(thiocarbonyldithio)-propan-1-ol (18 mg), $[\alpha]_D^{23}$ +25·5° (*c* 0·3), $\nu_{max.}$ 1085 and 3375 cm^{-1}.

(*c*) The epoxide was prepared from the allyl compound by the above procedure, but was not subjected to any purification after isolation from the washed and dried chloroform solution. The crude product (11·0 g) was added to a mixture of carbon disulphide (90 ml) and potassium hydroxide (13 g) in methanol (280 ml). After being boiled under reflux for 3 h the solution afforded the trithiocarbonate (3) (4·35 g), isolated by column chromatography (ether–chloroform, 1 : 1). Acidic hydrolysis of a portion (1·24 g), under the conditions specified above, gave 2,3-(thiocarbonyldithio)propan-1-ol (0·32 g), $[\alpha]_D^{25}$ +108·5° (*c* 1·4).

2,3-(*Carbonyldithio*)*propyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucoside* (4).—A mixture of 2,3-(thiocarbonyldithio)propyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside [preparation (*c*)] (0·65 g), mercury(II) acetate (1·23 g), and acetic acid (15 ml) was stirred at 40—45° for 30 min, then cooled, diluted with chloroform, filtered, and poured into water. The chloroform layer was removed and subsequently added to chloroform extracts of the aqueous portion, the combined organic solutions then being washed with aqueous sodium hydrogen carbonate and with water. Evaporation of the dried extract, followed by t.l.c. (ether) gave the *dithiocarbonate* (0·60 g), m.p. 120—122° (from chloroform–petroleum), $[\alpha]_D^{22}$ −2·1° (*c* 0·4), $\nu_{max.}$ 1650 and 1750 cm^{-1}, τ 4·7—6·5 (12H, m) and 7·90, 7·93, 7·97, and 8·00 (12H, 4s, 4 OAc) (Found: C, 45·0; H, 5·0; S, 13·4. $C_{18}H_{24}O_{11}S_2$ requires C, 45·0; H, 5·0; S, 13·3%).

2,3-(*Bisacetylthio*)*propyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucoside* (8).—The preceding dithiocarbonate (0·24 g) was added to a solution prepared from sodium (35 mg) and dry methanol (15 ml). The mixture was set aside, under nitrogen, for 1 h, and was then evaporated to a syrup, which was treated with acetic anhydride (3 ml) and pyridine (8 ml) at ambient temperature overnight. Dilution with water and extraction with chloroform gave, after evaporation of the washed and dried extracts and purification of the residue by t.l.c. (ether), the hexa-acetyl compound (0·20 g), m.p. 82—83° (from ether–petroleum), $[\alpha]_D^{23}$ −25·2° (*c* 0·35 in MeOH), $\lambda_{max.}$ 232 nm (ε 8040), $\nu_{max.}$ 1685 and 1750 cm^{-1}, τ 4·5—5·2 (3H, m), 5·2—5·6 (1H, m), 5·6—5·9 (2H, m), 5·9—6·4 (4H, m), 6·6—7·1 (2H, m), 7·65 (6H, s, 2 SAc), and 7·92 and 7·98 (12H, 2s, 4 OAc) (lit.,[6] m.p. 75—77°, $[\alpha]_D^{18}$ −26°).

2,3-*Epoxypropyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucoside*.—Allyl 2,3,4,6-tetra-O-acetyl-α-D-glucoside [6] (2·0 g) on treatment for 4 days with 0·2M-perbenzoic acid in chloroform (80 ml), followed by work-up as described for the β-isomer and purification by t.l.c. (ether), gave the epoxide (1·5 g), $[\alpha]_D^{22}$ +108° (*c* 1·7), τ 4·4—7·6 (12H, m) and 7·90 and 7·95 (12H, 2s, 4 OAc) (lit.,[3] $[\alpha]_D^{30}$ +114°).

2,3-(*Thiocarbonyldithio*)*propyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucoside*.—The preceding epoxide (4·2 g; prepared with omission of the purification stage), carbon disulphide (33 ml), potassium hydroxide (4·75 g), and dry methanol (120 ml) were boiled together under reflux for 1 h. The product, isolated as described for the β-isomer, was purified by t.l.c. (chloroform) to give the *trithiocarbonate* (0·46 g) as a yellow oil, $[\alpha]_D^{21}$ +111° (*c* 1·1), $\nu_{max.}$ 1740 cm^{-1}, τ 4·5—6·9 (12H, m) and 7·90, 7·93, 7·96, and 7·98 (12H, 4s, 4 OAc) (Found: C, 43·75; H, 5·0; S, 19·15. $C_{18}H_{24}O_{10}S_3$ requires C, 43·5; H, 4·9; S, 19·4%).

Hydrolysis of this trithiocarbonate (380 mg) with boiling 4N-hydrochloric acid (70 ml), and isolation of the aglycone as detailed above, gave 2,3-(thiocarbonyldithio)propan-1-ol (32 mg), $[\alpha]_D^{22}$ +6·1° (*c* 0·9).

2,3-(*Carbonyldithio*)*propyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucoside*.—Reaction of 2,3-(thiocarbonyldithio)propyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside (220 mg) with mercury(II) acetate (410 mg) in acetic acid (6 ml), under the conditions described for the β-isomer, gave the *dithiocarbonate*

[9] E. Fischer, *Z. physiol. Chem.*, 1919, **108**, 3; E. A. Talley, M. D. Vale, and E. Yanovsky, *J. Amer. Chem. Soc.* 1945, **67**, 2037.

(109 mg) as an oil, $[\alpha]_D^{21}$ +90° (*c* 0·7), $\nu_{max.}$ 1650 and 1740 cm^{-1} (Found: C, 45·05; H, 4·9; S, 13·2. $C_{18}H_{24}O_{11}S_2$ requires C, 45·0; H, 5·0; S, 13·3%).

2,3-(*Bisacetylthio*)*propyl* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucoside*.—The preceding dithiocarbonate (60 mg) was solvolysed in methanolic sodium methoxide, and the product was acetylated, as described for the β-isomer, to give the hexa-acetyl compound (27 mg), $[\alpha]_D^{21}$ +81° (*c* 0·3 in MeOH), $\nu_{max.}$ 1690 and 1745 cm^{-1}, τ 4·4—7·0 (12H, m), 7·70 (6H, s, 2 SAc) and 7·96 and 8·03 (12H, 2s, 4 OAc) (lit.,[6] $[\alpha]_D$ +88°).

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