302. *The Epoxide–Episulphide Transformation.*

By L. D. Hall, L. Hough, and R. A. Pritchard.

5,6-Dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (XIV) has been prepared from 5,6-anhydro-1,2-*O*-isopropylidene-α-L-idofuranose (VIII), by reaction with thiourea. The α-L-*ido*-isomer (XII) was similarly prepared from 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (V). Cyclisation of 6-acetylthio-6-deoxy-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose (XI) with sodium methoxide gave the L-*ido*-episulphide, thus confirming that the epoxide–episulphide transformation proceeds with inversion. Desulphurisation of the above 5,6-episulphides and their 5,6-trithiocarbonates afforded 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (XIII), which was identical with that prepared by hydrogenation of 5,6-didehydro-5,6-dideoxy 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (IX). Opening of the 5,6-episulphide ring by acid and by alkali is discussed.

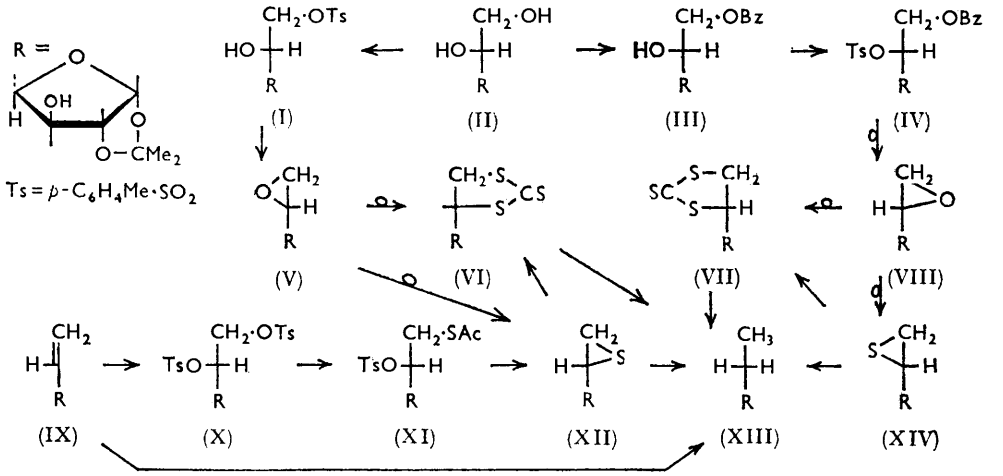
Interest in 5-deoxy-5-mercapto-D-glucose and the possibility that intramolecular reaction of the carbonyl group with the thiol group would give a six-membered cyclic hemiacetal analogous to the pyranose forms of D-glucose, caused us to investigate the preparation of 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (XIV) and the corresponding L-*ido*-isomer (XII), and their subsequent ring opening.

It is well known that an epoxide can be converted, probably with inversion, into an episulphide [1] by treatment with an alkali-metal thiocyanate or a thiourea. Consequently the preparation of 5,6-anhydro-D-glucose (V) and 5,6-anhydro-L-idose (VIII) derivatives from 6-*O*-tosyl (I) and 6-*O*-benzoyl-5-*O*-tosyl (IV) derivatives of 1,2-*O*-isopropylidene-α-D-glucofuranose respectively was examined. Although the precautions suggested by Tipson [2] were observed attempts to prepare the 5-*O*-tosyl (IV) and the 5-*O*-methanesulphonyl derivative of 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose by the method

[1] (*a*) Dachlauer and Jackel, G.P. 636,708/1936; (*b*) Culvenor, Davies, and Pausacker, *J.*, 1946, 1050; (*c*) Snyder, Stewart, and Ziegler, *J. Amer. Chem. Soc.*, 1947, **69**, 2672; (*d*) Culvenor, Davies, and Heath, *J.*, 1949, 278; (*e*) Goodman, Benitez, and Baker, *J. Amer. Chem. Soc.*, 1958, **80**, 1680.

[2] Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 107.

of Ohle and Dickhauser [3] were unsuccessful, almost quantitative recoveries of starting material being obtained. The sulphonylation was successfully achieved by a method communicated to us by Professor L. von Vargha,[4] the essential points being the extreme concentration of the reaction solution, the use of solid toluene-*p*-sulphonyl chloride, and the



extreme mildness of the purification procedure. An alternative method for the preparation of the 5-*O*-tosyl derivative (IV) was suggested [5] by the successful reduction of 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranurono-6 ⟶ 3-lactone with lithium aluminium hydride to 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-glucofuranose. 1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-glucofuranurono-6 ⟶ 3-lactone was prepared from the easily accessible D-glucofuranurono-6 ⟶ 3-lactone, but this derivative, and the corresponding 5-*O*-methanesulphonyl derivative, resisted reduction by a variety of reagents, including potassium and lithium borohydride, lithium aluminium hydride, and hydrogen in the presence of catalysts. This inactivity was probably due to a combination of steric hindrance, which inhibits the approach of the attaching group (*e.g.*, BH_4^-), and electronic factors which decrease the cationoid character of the carbonyl-carbon atom.

The epoxide–episulphide transformation was then studied by treatment of the 5,6-anhydro-compounds (V and VIII) with potassium thiocyanate, or with thiourea under varying conditions (Table 1). At first, reaction solutions containing 10% or more of the 5,6-anhydro-compound (V) were used, but this resulted in low yields of the episulphide (XII), and the formation of a gum, which was presumed to be polymeric since it was insoluble in both water and chloroform. It was shown that this polymerisation was due solely to a concentration effect, and not to either photosensitivity or aerial oxidation of the product: increased yields (>75%) of episulphides were obtained, with no polymerisation, when the concentration anhydro-compound was reduced to ~3%. It is noteworthy that Culvenor, Davies, and Savige [6] found that polymerisation of ethylene sulphides cannot be checked by ordinary antioxidants such as quinol.

Desulphurisation of the episulphides with Raney nickel gave 5,6-dideoxy-1,2-*O*-isopropylidene-D-*xylo*-hexofuranose (XIII) in both cases (see below), proving that they were isomeric 5,6-episulphides and that no migration to give, for example, a 3,6-episulphide had occurred.

Previous evidence [6,7] suggested that the reaction is accompanied by Walden inversion,

[3] Ohle and Dickhauser, *Ber.*, 1925, **58**, 2593.
[4] von Vargha, personal communication.
[5] Jones, *Canad. J. Chem.*, 1956, **34**, 310.
[6] Culvenor, Davies, and Savige, *J.*, 1952, 4480.
[7] Ettlinger, *J. Amer. Chem. Soc.*, 1950, **72**, 4792; van Tamelen, *ibid.*, 1951, **73**, 3444; Goodman and Baker, *ibid.*, 1959, **81**, 4924; Price and Kirk, *ibid.*, 1953, **75**, 2396; Bordwell and Andersen, *ibid.*, 1953, **75**, 4959; Reynolds, *ibid.*, 1957, **79**, 4951.

TABLE 1. *The epoxide–episulphide transformation.*

Starting isomer	Epoxide (g.)	Concn. (%)	Reaction time (hr.)	Temp.	Reagent	Yield (%)
D-*gluco*- (V)	0·2	10	1	50°	KCNS	5
	3·1	15	1	50	,,	30
	0·5	10	22	20	$CS(NH_2)_2$	33
	0·2	2·5	8	20	,,	78
	9·5	3·0	24	20	,,	75
L-*ido*- (VIII)	0·2	2·5	48	20	,,	78
	1·0	2·5	48	27	,,	79
	3·4	2·5	48	27	,,	76

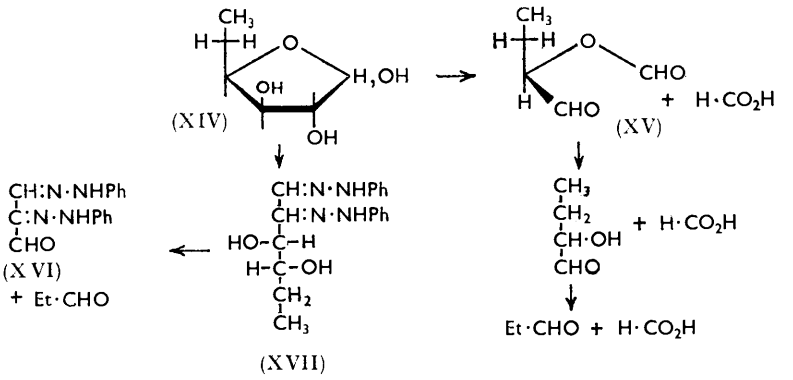
but confirmation of this for the epoxide–episulphide transformation was felt to be desirable. Cyclisation of 3,5-di-*O*-acetyl-6-acetylthio-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose to the L-*ido*-episulphide (XII) was attempted, but in agreement with Creighton and Owen [8] neither methanolic sodium methoxide nor aqueous sodium hydroxide was satisfactory. Since the toluenesulphonyloxy-group is a better " departer " than the acetoxy-group, cyclisation of 6-acetylthio-6-deoxy-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose (XI) was likely to be more successful. Replacement of the primary toluene-*p*-sulphonyloxy-group in 1,2-*O*-isopropylidene-5,6-di-*O*-tosyl-α-D-glucofuranose (X) by treatment [9] with potassium thiolacetate gave the acetylthio-derivative (XI) in 60% yield. Treatment of this compound with methanolic sodium methoxide gave an 89% yield of 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-L-idofuranose (XII), which was identical with that obtained by the reaction of thiourea and potassium thiocyanate with 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose, thus providing unequivocal proof that inversion had occurred during the epoxide–episulphide transformation. This confirms the observations of Creighton and Owen [8] who recently described a similar series of reactions.

McSweeney and Wiggins [10] prepared a crystalline 5,6-trithiocarbonate (VI) by heating a mixture of carbon disulphide, potassium hydroxide, and 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose in methanol and characterised the product by desulphurisation with Raney nickel to 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (XIII). In agreement with the suggestion [1b] that an episulphide (XII) acts as an intermediate in the formation of the trithiocarbonate, 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-L-idofuranose gave, with these reagents at *room temperature*, a high yield of the same trithiocarbonate. Since there must be an overall inversion of configuration at $C_{(5)}$, the product is 5,6-dideoxy-5,6-dithio-1,2-*O*-isopropylidene-α-L-idofuranose 5,6-trithiocarbonate (VI). This conclusion was reached independently by Creighton and Owen.[8] When this reaction was applied to the isomeric 5,6-anhydro- (VIII) and 5,6-episulphide (XIV) derivatives, similar results were obtained although the yellow 5,6-trithiocarbonate (VII) was contaminated with a colourless impurity which could not be removed. Culvenor, Davies, and Pausacker [1b] also obtained from cyclohexene oxide a trithiocarbonate which contained an unidentified white impurity.

Desulphurisation of each of the episulphides (XII, XIV), and the trithiocarbonates (VI, VII), gave the same product, namely, 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (XIII). McSweeney and Wiggins [10] also obtained this compound (m. p. 78°, $[\alpha]_D$ −31·4°) by reductive desulphurisation of the L-*ido*-trithiocarbonate (VI), but offered no structural proof other than the method of preparation. English and Levy,[11] however, obtained by the catalytic hydrogenation of 3-*O*-benzyl-5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*hexofuranose a product which had m. p. 79·0—79·6°. $[\alpha]_D$ −21·9°, and gave a depression of m. p. on admixture with McSweeney and Wiggins's compound. They then established the structure of their isopropylidene derivative by hydrolysis to the free

[8] Creighton and Owen, *J.*, 1960, 1024.
[9] Chapman and Owen, *J.*, 1950, 579.
[10] McSweeney and Wiggins, *Nature*, 1951, **168**, 874.
[11] English and Levy, *J. Amer. Chem. Soc.*, 1956, **78**, 2846.

sugar and subsequent periodate oxidation, in which 3 mol. of oxidant were consumed with the formation of propionaldehyde. English and Levy suggested that McSweeney and Wiggins's compound might be an isomer, formed by some rearrangement during preparation of the trithiocarbonate.

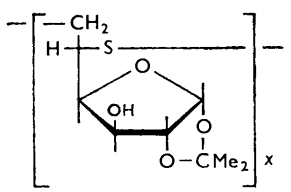


A specimen of English and Levy's dideoxy-compound (XIII), kindly provided by Professor J. English, gave no depression in m. p. with our specimen prepared by the method of McSweeney and Wiggins. Identity of these samples was confirmed by comparison with another specimen prepared by the hydrogenation of 5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (IX). [The compound (IX) was obtained crystalline by treating 1,2-*O*-isopropylidene-5,6-di-*O*-tosyl-α-D-glucofuranose with sodium iodide, by a modification of Oldham and Rutherford's method.[12]]

Acid-hydrolysis of the isopropylidene derivative (XIII) gave a reducing sugar (XIV) which rapidly (1 hr.) consumed 2 mol. of periodate, giving 1 mol. of formic acid, and then slowly (24 hr.) a third mol., liberating a further 2 mol. of acid. Propionaldehyde was isolated and characterised as its 2,4-dinitrophenylhydrazone. These results are consistent with the oxidation of a 5,6-dideoxyhexose in the furanose form (XIV) to a relatively stable intermediary formyl ester of 3,4-dideoxy-D-*glycero*-tetrose (XV), in agreement with the previous findings [13] that the stability of a formyl ester is related to the electrophilic character of the adjacent groups.

The structure of the 5,6-dideoxy-D-*xylo*-hexose (XIV) was verified by oxidising its phenylosazone (XVII) with sodium metaperiodate: mesoxalaldehyde 1,2-bisphenylhydrazone (XVI) was obtained [14] in high yield.

Attempted ring opening of the 5,6-episulphides by 0·1N-sodium hydroxide at room temperature yielded polymeric material which was insoluble in chloroform and in water. Culvenor, Davies, and Heath [1d] noted that the powerful polymerising action of sodium hydroxide and other strongly alkaline reagents was due to the opening of an episulphide ring to give the sodium derivative of the thiol, which then attacked another episulphide ring, thus rapidly giving a chain polymer. As expected from steric considerations, the tendency to polymerise was greater when the side-chain was small, and our findings are in agreement with this, since the 5,6-episulphides required *ca.* 15 hr. for complete polymerisation. Polymerisation resulted in a shift of the characteristic sulphide absorption from 206 to 230 mμ, without the formation of disulphide absorption at 300 mμ, and at no stage of the reaction was a positive thiol test obtained. This evidence, and the isolation of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose in good


(XVIII)

[12] Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366.
[13] Hough, Taylor, Thomas, and Woods, *J.*, 1958, 1212.
[14] Hough, Powell, and Woods, *J.*, 1956, 4799.

yield on desulphurisation of the polymer, was in agreement with a structure containing a repeating unit of 5,6-dideoxy-1,2-*O*-isopropylidene-*hexo*-furanose 5(6′)-sulphide (XVIII).

Acid-hydrolysis of the L-*ido*-episulphide (XII) with N-sulphuric acid at room temperature involved a complex change in rotation, a maximum value (+34°) being rapidly attained in 2½ hr. followed by a gradual decrease (to −6° in 48 hr.). The episulphide was shown by paper chromatography to give at least four components, the proportions varying with the reaction time. After partial hydrolysis (24 hr.), one fraction was separated on a cellulose column and identified as 5,6-dideoxy-5,6-epithio-L-idofuranose ($[\alpha]_D$ +33·3°). This reducing sugar was the initial product of the hydrolysis, its formation corresponding to the initial rapid increase in the optical rotation. Treatment of this compound with acid yielded a mixture containing the other three products of the original hydrolysate, which will be described later.

Experimental

Concentrations were carried out under reduced pressure. M. p.s were determined on a Kofler microscope stage. Optical rotations were determined for $CHCl_3$ solutions at 25° ± 1°. Paper chromatography was carried out on Whatman No. 1 filter paper by the descending method, with butan-1-ol–pyridine–water (10 : 3 : 3 v/v) as solvent, and rates of movement are quoted with reference to 2,3,4,6-tetra-*O*-methyl-D-glucose (R_G). Acylations were performed under rigorously anhydrous conditions, in apparatus dried at 100° and with purified reagents.

5,6-*Dideoxy*-5,6-*epithio*-1,2-O-*isopropylidene*-α-L-*idofuranose* (XII).—(a) *From* 5,6-*anhydro*-1,2-O-*isopropylidene*-α-D-*glucofuranose* (V). A solution of the anhydro-compound [15] (9·56 g.) and thiourea (3·6 g., 1·5 mol.) in methanol (250 ml.) was kept at room temperature, and the change in optical rotation observed: $[\alpha]_D$ −40° ⟶ −30° (constant; 10 hr.). After 24 hr. ice-water (350 ml.) was added, methanol removed by evaporation at room temperature, and the aqueous solution extracted several times with chloroform. The combined extracts were dried (Na_2SO_4) and concentrated, affording crystals, m. p. 162—165° (sublimes). Recrystallisation from light petroleum (b. p. 40—60°) gave the epithio-compound (XII) as needles (7·75 g., 75%), m. p. 167—169°, $[\alpha]_D$ −17·5° (*c* 3·1), sublimes at 80—130° (bath)/5 × 10^{-3} mm. (Found: C, 49·7; H, 6·6; S, 14·3. Calc. for $C_9H_{14}O_4S$: C, 49·5; H, 6·5; S, 14·7%). Paper chromatography gave a single white-centred spot (R_G 0·67; R_F 0·85) when sprayed with ammoniacal silver nitrate {lit.,[8] m. p. 164—165°, $[\alpha]_D$ −16° (*c*, 5)}. In one experiment the aqueous solution remaining after chloroform-extraction was concentrated to yield urea (66%), m. p. and mixed m. p. 126°.

(b) *From* 6-*acetylthio*-6-*deoxy*-1,2-O-*isopropylidene*-5-O-*tosyl*-α-D-*glucofuranose* (XI). Methanolic sodium methoxide [from sodium (0·102 g.) in dry methanol (5 ml.)] was added to a solution of the acetylthio-compound (1·87 g.) in chloroform (59 ml.) at −10° under anhydrous conditions. The resultant colloidal mass was shaken at −10° for 30 min., water (20 ml.) added, the chloroform layer removed, and the aqueous layer extracted with chloroform (3 × 10 ml.). The combined chloroform extracts were washed with water (3 × 30 ml.), dried ($CaSO_4$), and concentrated to a colourless solid (1·00 g.). This crystallised from chloroform–light petroleum (b. p. 60—80°) as needles of the epithio-compound (XII) (0·86 g., 89%), m. p. 166—168°. Further recrystallisation gave material of m. p. 169—170° (undepressed on admixture with the episulphide described above), $[\alpha]_D$ −17·6° (*c* 1·4). This product with acetic anhydride and pyridine gave 3-O-*acetyl*-5,6-*dideoxy*-5,6-*epithio*-1,2-O-*isopropylidene*-α-L-*idofuranose* as needles, m. p. 77—78° (sublimes) (Found: C, 51·2; H, 6·3; S, 10·5; Ac, 14·1. $C_{11}H_{16}O_5S$ requires C, 50·8; H, 6·2; S, 12·3; Ac, 16·5%).

1,2-O-*Isopropylidene*-5,6-*di*-O-*tosyl*-α-D-*glucofuranose* (X).—The ditosyl compound was prepared in 20% yield by the action of toluene-*p*-sulphonyl chloride on 1,2-*O*-isopropylidene-α-D-glucofuranose (method of Ohle and Dickhauser [16]). The yield was improved by the following procedure. 1,2-*O*-Isopropylidene-α-D-glucofuranose (10 g.) was mixed with benzene (40 ml.) and pyridine (20 ml.), and a solution of toluene-*p*-sulphonyl chloride (17·5 g., 2·01 mol.) in chloroform (35 ml.) was added at 0°. The yellow mixture was kept at room temperature for

[15] Mehltretter, Alexander, Mellies, and Rist, *J. Amer. Chem. Soc.*, 1951, **73**, 2424; Meyer and Reichstein, *Helv. Chim. Acta*, 1946, **29**, 139; Ohle and Vargha, *Ber.*, 1929, **62**, 2435.

[16] Ohle and Dickhauser, *Ber.*, 1925, **58**, 2593.

24 hr., then cooled to 0°, and water (10 ml.) was added dropwise, followed 30 min. later by 2N-hydrochloric acid (100 ml.). The aqueous layer was extracted with chloroform (2 × 150 ml.), the combined extracts were washed successively with 2N-hydrochloric acid (2 × 100 ml.), N-sodium hydrogen carbonate (100 ml.), and water (2 × 100 ml.), and dried (Na_2SO_4). Concentration produced a pale-yellow syrup which crystallised from ethanol as colourless needles (10 g.). Further crystallisation from ethanol gave the ditosyl compound (X) (9·3 g., 40%), m. p. 161—162° $[\alpha]_D$ −6·85° (*c* 2·7) (Found: C, 52·3; H, 5·65. Calc. for $C_{23}H_{28}O_{10}S_2$: C, 52·25; H, 5·35%) (lit.,[16] m. p. 160°, $[\alpha]_D$ −6·37°).

6-*Acetylthio*-6-*deoxy*-1,2-O-*isopropylidene*-5-O-*tosyl*-α-D-*glucofuranose* (XI).—The ditosyl compound (X) (1·865 g.) and potassium thiolacetate (0·861 g.) in ethyl methyl ketone (40 ml.) were heated under reflux for 1 hr. The mixture was concentrated to dryness, the residue fractionated between water (10 ml.) and chloroform (30 ml.), and the chloroform layer separated. The aqueous layer was extracted with chloroform (2 × 15 ml.), and the combined chloroform extracts were washed with water (20 ml.), dried ($CaSO_4$), and on concentration gave a yellow solid (1·558 g.). This was dissolved in methanol and decolorised (charcoal), and on evaporation the *acetylthio-compound* (XI) was obtained as needles (0·90 g., 60%), m. p. 139—140°, $[\alpha]_D$ +4·32° (*c* 1·5), $\nu_{max.}$ 1500, 1600 (Ph), 1693 (*S*-Ac), 3430 (OH) (Found: C, 50·15; H, 5·55. $C_{18}H_{24}O_8S_2$ requires C, 50·0; H, 5·6%).

6-O-*Benzoyl*-1,2-O-*isopropylidene*-5-O-*tosyl*-α-D-*glucofuranose* [4] (IV).—Toluene-*p*-sulphonyl chloride (33 g.) was added during 1 hr. to a stirred solution of the benzoyl compound [17] (VII) (50 g.) in pyridine (250 ml.) at 0° under rigorously anhydrous conditions. The mixture was kept at room temperature for 24 hr., the pyridine removed by distillation, and the residue dissolved in ether (200 ml.)–water (150 ml.) and filtered. The ether extract was washed with water, dried (Na_2SO_4), and evaporated, giving a syrup which crystallised from ethanol (70 ml.) as the tosyl derivative (IV) (15 g., 20%), m. p. 143—144° (Found: C, 57·8; H, 5·6. Calc. for $C_{23}H_{26}O_9S$: C, 57·7; H, 5·5%) (lit.,[16] m. p. 142°).

5,6-*Dideoxy*-5,6-*epithio*-1,2-O-*isopropylidene*-α-D-*glucofuranose* (XIV).—This compound was prepared from the anhydro-compound (Mehltretter *et al.*[15]) (VIII) by the method described above for the L-*ido*-isomer, the mixture taking 48 hr. to reach constant optical rotation. The crude crystalline compound had m. p. 138—140° (sublimes) and was purified by sublimation at 80—130° (bath)/5 × 10^{-3} mm., to give the *compound* (XIV) as needles (78·5%), m. p. 139—142°, $[\alpha]_D$ −76·2° (*c* 1·9) (Found: C, 49·5; H, 6·8; S, 14·65. $C_9H_{14}O_4S$ requires C, 49·5; H, 6·5; S, 14·7%).

The 5,6-episulphides give brilliant yellow solutions in concentrated sulphuric acid; no similar behaviour was observed with any of the precursors of either isomer.

5,6-*Dideoxy*-1,2-O-*isopropylidene*-5,6-*dimercapto*-α-L-*idofuranose* 5,6-*Trithiocarbonate* (VI).—(a) *From* 5,6-*anhydro*-1,2-O-*isopropylidene*-α-D-*glucofuranose*. A solution of the anhydro-compound (V) (0·10 g.), potassium hydroxide (0·07 g.), and carbon disulphide (0·1 ml.) in methanol (5 ml.) was heated under reflux for 2 hr., then poured into ice-water, giving the xanthate (VI) (0·095 g., 70%), m. p. 177—178°. After recrystallisation from aqueous ethanol this had m. p. 178—179°, $[\alpha]_D$ +2° (*c* 1·08), $\lambda_{max.}$ 316 mμ (ε 14,000) (Found: C, 40·6; H, 5·0. Calc. for $C_{10}H_{14}O_4S_3$: C, 40·8; H, 4·8%).

(b) *From* 5,6-*dideoxy*-5,6-*epithio*-1,2-O-*isopropylidene*-α-L-*idofuranose*. A mixture of this sulphide (0·019 g.) with potassium hydroxide (0·018 g.) and carbon disulphide (0·02 ml.) in methanol (10 ml.) was kept at room temperature for 24 hr., then poured into ice-water, and the crystalline product collected and purified as before (0·0192 g., 75%), m. p. and mixed m. p. 178—179° (lit.,[10] m. p. 179·5—180·5°).

5,6-*Dideoxy*-1,2-O-*isopropylidene*-5,6-*dimercapto*-α-D-*glucofuranose* 5,6-*Trithiocarbonate* (VII).—Attempts to prepare this compound from 5,6-anhydro-1,2-*O*-isopropylidene-α-L-idofuranose and 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose, using the methods (a) and (b) described for the L-*ido*-isomer gave an impure product ($[\alpha]_D$ of samples varied from −100° to −250°, whilst the m. p. varied between 198° and 210°). It ran on chromatograms with the L-*ido*-isomer and gave a white spot (R_G 0·69) on a brown background with the silver nitrate spray. It had a characteristic trithiocarbonate absorption in the ultraviolet region (λ_{max} 316 mμ).

5,6-*Dideoxy*-1,2-O-*isopropylidene*-α-D-xylo-*hexofuranose* (XIII).—5,6-Dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-L-idofuranose (0·60 g.) and Raney nickel (*ca.* 2 g.) were heated under

[17] Ohle, *Ber.*, 1924, **57**, 403.

reflux in ethanol (30 ml.) for 3 hr. Filtration and concentration gave crystals which recrystallised from light petroleum (b. p. 60—80°) as needles (0·370 g., 72%), m. p. 77—78° (sublimes), mixed m. p. with an independent sample [11] 77—79°, $[\alpha]_D$ −26·3° (*c* 3·08) (Found: C, 57·7; H, 8·3. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%) (lit.,[10,11,18] m. p. 78·7—79·5°, $[\alpha]_D$ −21·9°; $[\alpha]_D$ −31·4°).

Similar treatment of 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose, 5,6-dideoxy-1,2-*O*-isopropylidene-5,6-dimercapto-α-L-idofuranose 5,6-trithiocarbonate (VI), and 5,6-dideoxy-1,2-*O*-isopropylidene-5,6-dimercapto-α-D-glucofuranose 5,6-trithiocarbonate (VII) gave products identical with (XIII) in m. p., mixed m. p., opical rotation, and *X*-ray powder photographs.

5,6-*Didehydro*-5,6-*dideoxy*-1,2-O-*isopropylidene*-α-D-xylo-*hexofuranose* (IX).—1,2-*O*-Isopropylidene-5,6-di-*O*-tosyl-α-D-glucofuranose (1·70 g.) and sodium iodide (3·0 g.) were heated under reflux for 1½ hr., in dry ethyl methyl ketone (50 ml.). The precipitated sodium toluene-*p*-sulphonate was filtered off, washed with ethyl methyl ketone, dried at 70°, and weighed (1·24 g., 100%). Concentration of the combined filtrates produced a brown residue which was fractionated between aqueous sodium thiosulphate (5 g. in 50 ml.) and chloroform (30 ml.). The aqueous layer was then extracted with chloroform (2 × 30 ml.), and the combined chloroform extracts were washed with water, and dried ($CaSO_4$). Concentration produced a yellow syrup, a methanolic solution of which was decolorised with charcoal and concentrated to a solid (0·541 g., 92·5%), m. p. 59—63°, which contained no sulphur (Lassaigne test). Sublimation at 70° (bath)/10^{-3} mm. afforded needles of 5,6-*didehydro*-5,6-*dideoxy*-1,2-O-*isopropylidene*-α-D-xylo-*hexofuranose* (0·50 g., 85%), m. p. 61—65°, $[\alpha]_D$ −51·5° (*c* 1·1), $\nu_{max.}$ 920, 1420, 1644, 1884, 3030, 3080 (monosubstituted ethylene derivative), 3430 (OH) (Found: C, 57·95; H, 7·8. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%).

5,6-*Dideoxy*-1,2-O-*isopropylidene*-α-D-xylo-*hexofuranose* (XIII).—The unsaturated derivative (IX) (0·1098 g.) was hydrogenated at atmospheric pressure in absolute ethanol (20 ml.), with 10% palladium–charcoal (0·144 g.) (uptake 25·7 ml. in 1 hr., 1·03 mol.). The catalyst was filtered off and washed with ethanol, and the combined filtrates were concentrated, affording crystals (0·199 g., 99·5%), m. p. 60—64°. Recrystallisation from light petroleum (b. p. 60—80°) afforded 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose as plates (0·1909 g., 95%), m. p. 60—64·5°, $[\alpha]_D$ −22·5° (*c* 1·1). The plates changed to needles at room temperature, and the m. p. increased to 70—74° (12 days). A sample purified by vacuum-sublimation at 70° (bath)/10^{-3} mm. had m. p. 77—78°, and mixed m. p. with sample prepared by English and Levy,[11] 77—79°.

5,6-*Dideoxy*-D-xylo-*hexofuranose* (XIV).—5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (0·093 g.) was heated in 0·1N-hydrochloric acid (10 ml.) at 95—100° to constant optical rotation (0·5 hr.). The solution was neutralised with Amberlite resin IR-4B(OH^-), and concentrated to a syrup, which showed a single spot (R_G 0·59) on paper chromatograms with both the silver nitrate and the *p*-anisidine hydrochloride sprays.[19]

Periodate Oxidation of 5,6-*Dideoxy*-D-xylo-*hexofuranose*.—5,6-Dideoxy-D-*xylo*-hexofuranose (0·028 g.) was dissolved in 0·09M-sodium metaperiodate (100 ml.) and stored in the dark alongside a blank solution containing no sugar derivative. At intervals, aliquot portions (5 ml.) were added to a mixture of phosphate buffer (pH 6·9; 15 ml.) and 20% potassium iodide solution (2 ml.), and the liberated iodine was titrated with 0·1N-sodium thiosulphate (starch indicator). Aliquot portions (5 ml.) were also taken for formic acid estimation, mixed with ethylene glycol (2 ml.), left for 15 min., and titrated potentiometrically to pH 6·28.[20]

The " fugitive end-point " encountered during these titrations indicated the presence of a formyl ester in solution: [21]

Time (hr.)	1	2½	4½	24
Periodate uptake (mol.)	2·2	2·3	2·4	2·72
Formic acid (mol.)	1·45	1·67	1·90	2·56

The remaining periodate oxidation solution was extracted several times with ether, and the combined ether extracts were treated with Brady's reagent (1·5 ml.). Concentration gave a

[18] Jones and Thompson, *Canad. J. Chem.*, 1957, **35**, 955.
[19] Hough, Jones, and Wadman, *J.*, 1949, 2511; 1950, 1702.
[20] Anderson, Greenwood, and Hirst, *J.*, 1955, 225.
[21] Morrison, Kuyper, and Orten, *J. Amer. Chem. Soc.*, 1953, **75**, 1502.

mixture of crystals which were dissolved in chloroform and fractionated on a column of bentonite–kieselguhr,[22] with ethanol–chloroform (1 : 5 v/v), to give propionaldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 154°.

5,6-*Dideoxy*-D-threo-*hexosazone*.[23]—A mixture of 5,6-dideoxy-D-*xylo*-hexofuranose (0·05 g.), water (1 ml.), acetic acid (0·5 ml.), and phenylhydrazine (0·22 ml.) was heated at 95—100° for 45 min. The crystalline product was filtered off, washed with cold water and cold benzene, and dried, giving the phenylosazone (XVII) as yellow needles (0·055 g.), m. p. 163—165°.

Periodate Oxidation of 5,6-*Dideoxy*-D-threo-*hexosazone*.—Without further purification, the osazone (XVII) was dissolved in 70% ethanol (10 ml.), mixed with 0·3M-sodium metaperiodate (2 ml.), and left at room temperature for 2 hr. The bright orange precipitate was collected on a sintered-glass filter, washed with water, and dried. Recrystallisation from ethanol–water gave mesoxalaldehyde 1,2-bisphenylhydrazone (XVI) (0·068 g.), m. p. and mixed m. p. 195—196°. The ultraviolet absorption of this product was identical with that of an authentic specimen, prepared by periodate oxidation of D-*arabo*-hexose phenylosazone.

TABLE 2. *Attempted reduction of lactone derivatives.*

Reagent nature	mol.	Solvent	Time (hr.)	Temp.	Product *	Ref.
KBH_4	1·8	Aq. dioxan	18	20°	Acid syrup	25
$LiBH_4$	5	Dioxan	24	20	—	26
$LiBH_4$	4	Tetrahydrofuran	24	50	—	
$LiAlH_4$	1·1	Ether	1	35	—	
$LiAlH_4$	7	Tetrahydrofuran	2½	70	Acid syrup	
KBH_4–NaOMe	2	Methanol	24	20	,,	27
KBH_4–H_3BO_3	1·1	Methylcellosolve–water	4	20	,,	
KBH_4–HOAc	5	,, ,,	6	20	,,	28
H_2–Pt_2O (200 lb./in.²)			7	100	,,	29

* The recovered starting material (indicated —) was characterised by mixed m. p., specific rotation, and paper chromatography with the lactone spray.[30] The acidic syrups were investigated by paper chromatography, separation on alumina, acetylation, and attempted conversion into the desired 5,6-anhydro-compound by sodium methoxide; no homogeneous compound was obtained.

1,2-O-*Isopropylidene*-5-O-*tosyl*-α-D-*glucofuranurono*-6 ⟶ 3-*lactone*.[5]—Toluene-*p*-sulphonyl chloride (35 g.) in pyridine (75 ml.) was added to 1,2-*O*-isopropylidene-α-D-glucofuranurono-6 ⟶ 3-lactone [24] (33 g.) in pyridine (150 ml.). The mixture was kept at room temperature for 24 hr., then poured on ice, and the resultant crystals were filtered off, washed with water, and dried. Recrystallisation from methanol gave the tosyl-lactone (38 g., 74%), m. p. 185—193°, $[\alpha]_D$ +80° (*c* 1·03 in Me_2CO) (Found: C, 51·5; H, 5·1. Calc. for $C_{16}H_{18}O_8S$: C, 51·9; H, 4·9%).

1,2-O-*Isopropylidene*-5-O-*methanesulphonyl*-α-D-*glucofuranurono*-6 ⟶ 3-*lactone*.—This *lactone* was prepared in the same way as the tosyl derivative, but by using methanesulphonyl chloride (1·1 mol.). It (75%) recrystallised from methanol as needles, m. p. 155—157°, $[\alpha]_D$ +65·5° (*c* 2·02 in Me_2CO) (Found: C, 41·0; H, 5·1. $C_{10}H_{14}O_8S$ requires C, 40·8; H, 4·8%).

Reduction of the Above Lactones.—Attempts to reduce the 5-*O*-tosyl- and 5-*O*-methanesulphonyl-1,2-*O*-isopropylidene-α-D-glucofuranurono-6 ⟶ 3-lactone to the corresponding D-glucofuranose derivatives were made: the details are in Table 2.

Attempted Alkaline Hydrolysis of the Episulphides.—(1) A solution of the L-*ido*-isomer (XII) in 0·1N-methanolic sodium hydroxide was kept at room temperature, and the change of optical rotation observed: $[\alpha]_D$ −15° ⟶ −48° (constant; 24 hr.). When the solution was neutralised with dilute sulphuric acid, the bulk of the reactants separated as a gum which appeared to be polymeric, gave a negative thiol test with sodium nitroprusside, and failed to decolorise iodine solution. Concentration of the mixture under nitrogen, with omission of the neutralisation, failed to yield the sodium salt of the thiol.

[22] Meigh, "Modern Methods of Plant Analysis," Springer Verlag, Berlin, 1955, Vol. II, p. 427.
[23] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1946, **68**, 1766.
[24] Owen, Peat, and Jones, *J.*, 1941, 339.
[25] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.
[26] Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York, 1956, p. 510.
[27] Frush and Isbell, *J. Amer. Chem. Soc.*, 1956, **78**, 2844.
[28] Wolfrom and Anno, *J. Amer. Chem. Soc.*, 1952, **74**, 5583.
[29] Glattfeld and Stack, *J. Amer. Chem. Soc.*, 1937, **59**, 753.
[30] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

Desulphurisation of the gum with Raney nickel gave a good yield of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose, m. p. and mixed m. p. 75—77°, and acid-hydrolysis of the latter afforded 5,6-dideoxy-D-*xylo*-hexofuranose (R_G 0·59).

(2) Similar treatment of the D-*gluco*-isomer (XIV) produced a water-insoluble polymer, and a change in optical rotation: $[\alpha]_D$ −73° ⟶ −7° (constant; 24 hr.).

Acid-hydrolysis of the 5,6-*Episulphides.*—5,6-Dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-L-idofuranose (2 g.) was dissolved in dioxan (62·5 ml.) and 2N-sulphuric acid (62·5 ml.), the change in optical rotation being followed polarimetrically at 37°: $[\alpha]_D$ +16·25° (½ hr.), +37·5° (2½ hr.), +36·2° (4½ hr.), 32·2° (6¼ hr.), 3·74° (24 hr.). The solution was neutralised with barium carbonate, filtered, and concentrated to a pale-brown syrup which was shown by paper chromatography to contain major components at R_G 0·5 and 0·27, and minor components at R_G 0·15 and 0·11. This syrup was separated on a cellulose column (3·25 × 25 cm.), with butanol half-saturated with water as the mobile phase, into four components: (i) R_G 0·5 (300 mg.), $[\alpha]_D$ +33·3°; (ii) R_G 0·27 (850 mg.), $[\alpha]_D$ −10·8°; (iii) R_G 0·15 (163 mg.); (iv) R_G 0·11 (98 mg.). The total recovery from the column, including the imperfectly separated fractions, was 88%.

Investigation of hydrolysis fraction (i) (R_G 0·5). This syrup reduced Fehling's solution, whereas its precursor did not, and gave a negative thiol test with sodium nitroprusside. Further acid-hydrolysis with 2N-sulphuric acid gave a syrup which showed on a paper chromatogram all four spots of the original hydrolysis mixture. In the same way it was shown that the spot of R_G 0·5 disappeared completely on treatment with 5N-sulphuric acid (24 hr.), to the accompaniment of a large change in specific rotation: $[\alpha]_D$ −6 ⟶ +35°.

A portion of the syrup (38 mg.) was dissolved in dry acetone (100 ml.) containing concentrated sulphuric acid (1 drop), and shaken with anhydrous copper sulphate (2 g.) at room temperature for 48 hr. The mixture was neutralised with ammonia (*d* 0·880), filtered, and concentrated, to give crystals (29 mg.), m. p. 120—135° (sublimes). These recrystallised from chloroform–light petroleum (b. p. 40—60°) and, after vacuum-sublimation, formed needles of 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-L-idofuranose (22·4 mg.), m. p. and mixed m. p. 167—169°, the R_G value and infrared spectrum being identical with those of an authentic specimen.

Another portion of this compound (85·8 mg.) in 70% ethanol (20 ml.) was heated under reflux with Raney nickel (*ca.* 2 g.) for 1 hr. The solution was then filtered and concentrated to a syrup (65 mg.), $[\alpha]_D$ 0 ± 3° (*c* 0·72 in H_2O), which did not reduce Fehling's solution and gave a single spot on a paper chromatogram (R_G 0·43) when sprayed with ammoniacal silver nitrate. This value was identical with that of a specimen of 5,6-dideoxy-D-*xylo*-hexitol, prepared by heating 5,6-dideoxy-D-*xylo*-hexofuranose under reflux with Raney nickel.

Periodate Oxidation of 5,6-*Dideoxy*-5,6-*epithio*-1,2-O-*isopropylidenehexoses.*—Aqueous solutions of these compounds (25 mg. in 100 ml.) were oxidised with 0·3M-sodium metaperiodate in unbuffered solution, as described earlier, giving the following results:

Time (hr.)		2	24	70	94	168
Periodate uptake	L-*ido*-isomer	0·94	1·62	2·62	2·6	2·66
	D-*gluco*-isomer	0·85	1·2	1·5	1·71	2·05

The acid liberated was titrated potentiometrically to pH 6·28 with 0·01N-sodium hydroxide. The L-*ido*-isomer produced 1 mol. (110 hr.); the D-*gluco*-isomer produced 0·5 mol. (110 hr.), rising to 0·7 mol. (160 hr.). After 70 hr. a chromotropic acid determination [31] showed that no formaldehyde was present in either oxidation solution.

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DEPARTMENT OF ORGANIC CHEMISTRY,
THE UNIVERSITY, BRISTOL, 8.

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[31] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.