Branched-chain Sugars. Part XIV.[1] Reactions of Some Glycosulose Derivatives with Diazomethane: Ring Expansion of Glycosulose Derivatives

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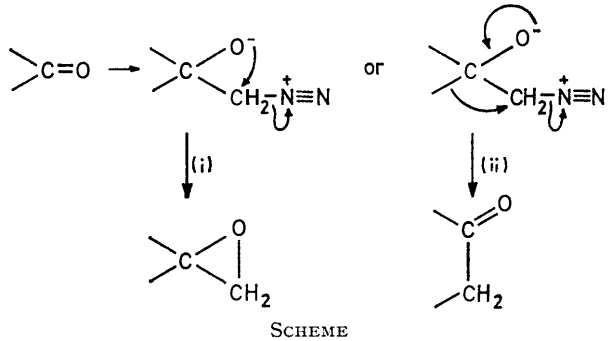
Epoxidation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (1) and of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (12) by treatment with diazomethane in methanol–ether has been shown to be accompanied by ring expansion (methylene insertion). The structures and configurations of the products have been established. Some aspects of the stereochemical course of the reactions are discussed.

THE reaction of diazomethane with aliphatic ketones is well known to yield either an epoxide by methylene addition across the carbonyl group [path (i)] or the next higher homologous ketone by α-methylene insertion on either side of the carbonyl group [path (ii)]: although this may not be true in every case [2] both products are usually considered to arise from the same initial diazomethane adduct (see Scheme). The preferred pathway depends on the nature of the ketone and the solvent,[3] and also on conformational effects.[4] Previously we have described the reaction of glycosiduloses with diazomethane to afford a mixture of isomeric epoxides formed by path (i).[5-7] Now we report the finding that under certain conditions some derivatives of glycosuloses give a mixture of epoxides which are formed either by path (i) or by sequential α-methylene insertion [path (ii)] followed by reaction of the new ketone so produced with more diazomethane according to path (i). The latter reaction pathway can furnish a simple method for the synthesis of branched-chain sugars having a deoxy-function adjacent to the branch point. Since preliminary

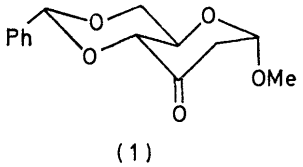


SCHEME

accounts of our work were reported [8,9] other reports of methylene insertion reactions in sugar derivatives have appeared.[4,10,11]

[1] Part XIII, A. D. Ezekiel, W. G. Overend, and N. R. Williams, *J. Chem. Soc.* (*C*), 1971, 2907.
[2] J. N. Bradley, C. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 1964, 4334; C. W. Cowell and A. Ledwith, *Quart. Rev.*, 1970, **24**, 119.
[3] H. Zollinger, 'Diazo and Azo Chemistry,' Interscience, New York, 1961, p. 71.
[4] T. D. Inch, G. J. Lewis, and R. P. Peel, *Carbohydrate Res.*, 1971, **19**, 29.
[5] J. S. Burton, W. G. Overend, and N. R. Williams, *Proc. Chem. Soc.*, 1962, 181; *J. Chem. Soc.*, 1965, 3433.
[6] W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 1965, 3446.
[7] W. G. Overend, A. C. White, and N. R. Williams, *Carbohydrate Res.*, 1970, **15**, 185.
[8] B. Flaherty, W. G. Overend, and N. R. Williams, *Chem. Comm.*, 1966, 434.
[9] Mrs. S. Nahar, W. G. Overend, and N. R. Williams, *Chem. and Ind.*, 1967, 2114.
[10] T. D. Inch, G. J. Lewis, R. P. Peel, and Mrs. N. Williams, *Chem. Comm.*, 1970, 1549.
[11] J. P. Horwitz, N. Mody, and R. Gasser, *J. Org. Chem.*, 1970, **35**, 2335.

Treatment of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (1)[12] with diazomethane in methanol–diethyl ether (3 : 2) afforded a multicomponent mixture of products from which methyl 1′,4-anhydro-5,7-*O*-benzylidene-2,3-dideoxy-4-*C*-hydroxymethyl-α-D-*ribo*-heptoside (2) was isolated as the major product by crystallisation from propan-2-ol. The residue from the mother liquors slowly crystallised to yield methyl 1′,3-anhydro-4,6-*O*-benzylidene-2-deoxy-3-*C*-hydroxymethyl-α-D-*arabino*-hexopyranoside (3) as a minor product.



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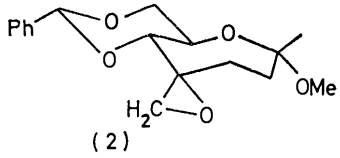

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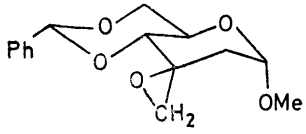

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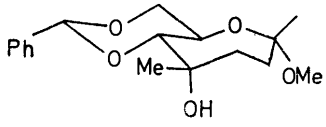

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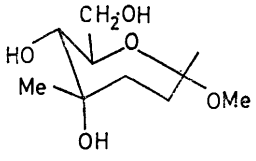

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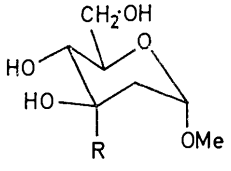


(6) R = H (7) R = Me

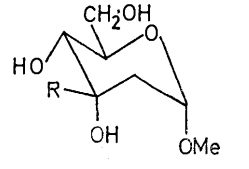
Evidence for the structure of compound (2) was obtained from its elemental analysis, its molecular weight as determined by epoxide assay, the liberation of benzaldehyde on acidification, a positive test for a 2-deoxy-sugar and an epoxide, and its n.m.r. spectrum. Besides the expected signals for phenyl, acetal, and methoxy-protons [τ 2·60 (5H), 4·50 (1H), and 6·63 (3H), respectively], one-proton doublets at τ 6·80 and 7·45 (*J* 7 Hz) could be assigned to the epoxide ring protons, a one-proton quartet at τ 5·30 was ascribable to the anomeric proton, and three- and one-proton multiplets centred at τ 8·0 and 8·80 could be assigned to the C-2 and C-3 methylene protons. The remaining four protons (H-5, H-6, H-7, and H-7′) gave a multiplet in the region τ 5·5—6·4. Further evidence for structure (2) was obtained by reduction with lithium aluminium hydride to yield methyl 5,7-*O*-benzylidene-2,3-dideoxy-4-*C*-methyl-α-D-*ribo*-heptoside (4), the n.m.r. spectrum of which, in comparison with that of the epoxide (2), showed the disappearance of the doublets at τ 6·8 and 7·45 and the appearance of a three-proton singlet at τ 8·65. This indicated the formation of a *C*-methyl group. A five-proton multiplet in the region τ 7·4—8·5 was assigned to the four methylene protons and one hydroxy-proton. Treatment of the *C*-methyl compound (4) with hydrogen over palladium–charcoal yielded methyl 2,3-dideoxy-4-*C*-methyl-α-D-*ribo*-heptoside (5), which consumed 1·01 mol. equiv. of sodium periodiate in 1 h thereby indicating the 2,3-dideoxy-4-*C*-methyl rather than the possible alternative 2,4-dideoxy-3-*C*-methyl structure, in accord with the expectation that the more nucleophilic carbon will migrate from C-3 to displace nitrogen in the initial intermediate.[13] The rapid consumption of periodate suggested a *cis*-configuration for the diol system, although this must remain a tentative conclusion in the absence of the isomeric *trans*-diol. More convincing evidence for the D-*ribo*-configuration of compound (5) was obtained by comparison of its electrophoretic mobility in borate buffer at pH 9·2 with those of reference compounds listed in Table 1. Compound (5) shows a similar mobility to compounds (8) and (9) with a *cis*-3,4-diol system, in contrast to the lower mobility of compounds (6) and (7) which have a corresponding *trans*-diol system.

TABLE 1

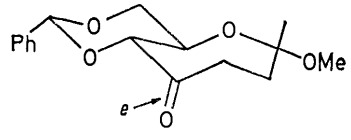
M_G Values of some glycosides in borate buffer (pH 9·2)

	M_G
Methyl 2-deoxy-α-D-*arabino*-hexopyranoside (6)	0·16
Methyl 2-deoxy-3-*C*-methyl-α-D-*arabino*-hexopyranoside (7) *	0·13
Methyl 2-deoxy-α-D-*ribo*-hexopyranoside (8)	0·24
Methyl 2-deoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (9) †	0·27
Compound (5)	0·30

* Prepared according to B. Flaherty (Ph.D. Thesis, University of London, 1965). † See Flaherty *et al.*[12]



(8) R = H (9) R = Me



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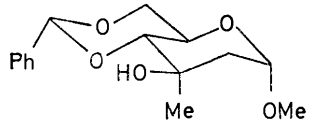

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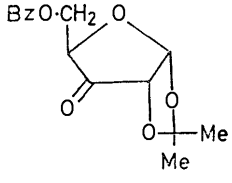


(12)

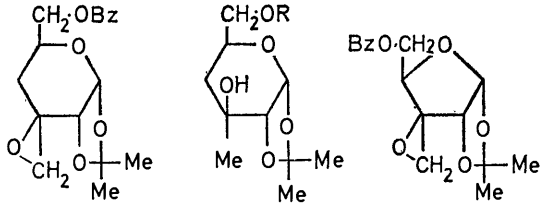
Formation of the *ribo*- rather than the *arabino*-epoxide from the intermediate heptosidulose may be rationalised by invoking preferential equatorial attack by diazomethane with the sugar in the conformation indicated in formula (10), although the preferred conformation for this seven-membered ring compound is a matter for speculation.

[12] B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc.* (*C*), 1966, 398.
[13] Ref. 3, p. 73.

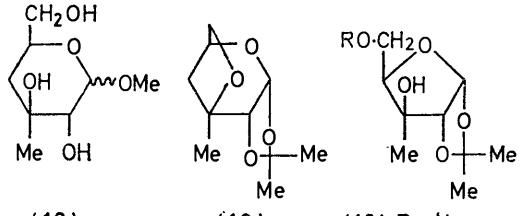
When the epoxide (3) was reduced with lithium aluminium hydride it gave a product (11) isomeric with the substance obtained from the reaction between the glycopyranosidulose (1) and methylmagnesium iodide.[12] As the latter product has been shown [12] previously to have the *ribo*-configuration, the new branched-chain glycoside (11) must belong to the *arabino*-series. This configurational assignment is supported by the n.m.r. spectrum of epoxide (3), by high-resolution i.r. spectral analysis [14] of the hydroxy-stretching region of the reduction product (11), and by periodate oxidation (1 mol. equiv. consumed in 10 h) and the M_G value (0·13 in borate buffer, pH 9·2) of the product from the debenzylidenation of compound (11).

Substitution of benzene or tetrahydrofuran for methanol in the reaction of the glycosidulose (1) with diazomethane led to the same mixture of products, as indicated by t.l.c., but with different amounts of compounds (2) and (3) [28 and 34%, respectively (yields of isolated material)]. Reaction in pure benzene was less satisfactory (20 and 2%, respectively).

A similar ring expansion of a pentofuranoid derivative has been achieved. Treatment of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (12) with diazomethane in methanol–diethyl ether (3 : 1) yielded, after separation of the multicomponent mixture of products by column chromatography on silica gel, 1′,3-anhydro-5-*O*-benzoyl-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-xylofuranose (14) (25%) and 1′,3-anhydro-6-*O*-benzoyl-4-deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (13) (65%). With diethyl ether alone as solvent, or with dioxan, tetrahydrofuran, or dimethyl sulphoxide instead of methanol, the



(13) (15) R = H (17) R = Ts (14)



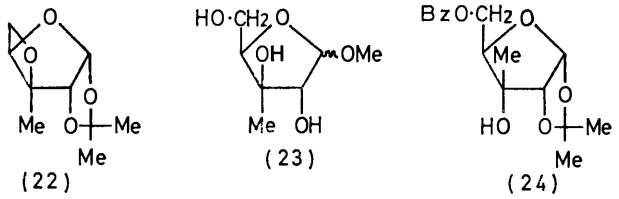
(16) (18) (19) R = H (20) R = Ts (21) R = Bz

major product was compound (14), and ring-expanded product was not detected in the reaction mixtures. The structure of compound (13) was indicated by its elemental analysis, molecular weight as determined by osmometry, and n.m.r. spectrum. Besides the expected signals for phenyl and methyl protons, one-proton doublets at τ 4·46 and 6·38 were ascribable to H-1 and H-2 ($J_{1,2}$ 5·0 Hz) and multiplets in the region τ 7·1—7·8 (three protons) and centred at τ 8·2 (one proton) were assigned to the four epoxide and C-4 methylene protons, H-5 and the two 6-protons appearing as a multiplet centred at τ 5·7; the total proton count was 20. In particular, the absence of any coupling between H-2 and a proton at C-3 suggests that methylene insertion occurred between C-3 and C-4 in the ulose (12), to give the 4-deoxy-3-*spiro*-epoxide, and not the 3-deoxy-4-*spiro*-epoxide isomer. Further support for this structural assignment was obtained by reduction of compound (13) with lithium aluminium hydride to give 4-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-*xylo*-hexopyranose (15), debenzoylation occurring concomitantly with epoxide cleavage. Treatment of this compound (15) with Amberlite resin (IR-120; H^+) in methanol yielded a syrupy methyl glycoside which only slowly consumed 1·03 mol. equiv. of sodium periodate, without production of formaldehyde, indicating a *trans*-diol consistent with a glycoside structure (16) but not with either the furanoside or pyranoside derivable from a 3-deoxy-4-*C*-methyl isomer. Further, a crystalline monotoluene-*p*-sulphonate (17) could be prepared from compound (15), and this ester (17) on treatment with sodium methoxide readily yielded an anhydro-sugar, considered to be 3,6-anhydro-4-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-*xylo*-hexopyranose (18) on the basis of its elemental analysis and n.m.r. spectrum. The ester (17) would be expected to be the primary 6-*O*-*p*-tolylsulphonyl derivative, since tertiary hydroxy-groups are known to be resistant to esterification under the basic conditions we employed. For this compound to yield an anhydro-sugar requires the hydroxy-group at C-3 and the *p*-tolylsulphonyloxymethyl group at C-5 to be *cis*, thus establishing the *xylo*-configuration for compounds (13) and (15)—(18).

Similar evidence was used to support the structure assigned to the epoxide (14). N.m.r. spectral analysis gave a total proton count of 18, with the expected peaks, and in particular an AB quartet (τ 6·79 and 6·95; *J* 4·5 Hz) ascribed to the epoxide methylene protons with no peaks in the region τ 7·0—8·3. Reduction of epoxide (14) with lithium aluminium hydride afforded crystalline 1,2-*O*-isopropylidene-3-*C*-methyl-α-D-xylofuranose (19), which gave crystalline mono-*O*-tosyl and mono-*O*-benzoyl derivatives [(20) and (21), respectively]. With sodium methoxide, the tosylate (20) afforded an anhydride considered to be compound (22), on the basis of its elemental analysis and i.r. spectrum. The formation of this anhydride indicates a *xylo*-configuration for compounds (14) and (19)—(22), since only in this configuration would the sequence of reactions for the conversion of the epoxide (14) into the anhydride (22) be feasible. Further evidence for this configuration was obtained by converting the 1,2-*O*-isopropylidene deriva-

[14] R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall, and N. R. Williams, *Proc. Chem. Soc.*, 1963, 133.

tive (19) into an αβ-mixture of methyl furanosides (23) with methanolic hydrogen chloride, and comparing its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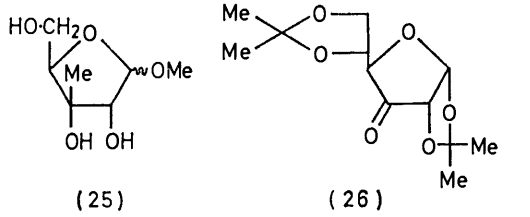
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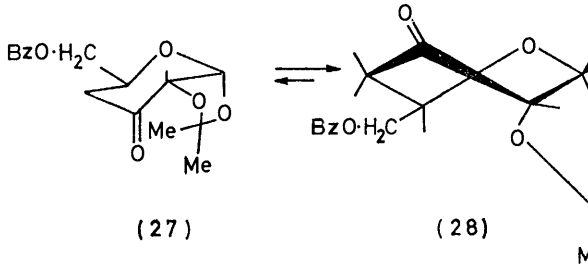
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(28)

rate of oxidation by sodium periodate (see Table 2) with that of the methyl αβ-furanoside mixture (25) which is epimeric with (23) at C-3 (see Table 2). Compound (25)

TABLE 2

Configurational evidence for compounds (21), (23), (24), and (25)

Compound	Consumption of periodate (mol. equiv.)	$\nu_{max.}$(CCl_4) cm^{-1}	R_F Solvent A [a]	R_F Solvent B [b]	Ratio
(21), (23) *xylo*	1·02 in 4·2 h at 35°	3628	0·18	0·14	0·8
(24), (25) *ribo*	1·04 in 0·5 h at room temp.	3535	0·37	0·74	2·0

[a] Paper chromatography: solvent butanol–ethanol–water (4 : 1 : 5) (organic phase). [b] Solvent A + 1% phenylboronic acid.

was derived from the 3-*C*-methyl sugar (24), which was obtained when the ulose (12) was treated with methylmagnesium iodide. Likewise treatment of the ulose (12) with methyl-lithium in tetrahydrofuran followed by replacement of the benzoyl group at C-5 also afforded compound (24) as the major product.

The results from the periodate oxidation studies indicate that the diol configuration in compound (23) is *trans* and that in (25) is *cis*, and incidentally confirm the furanoside structures assigned to these glycosides. This conclusion was borne out by the evidence summarised in Table 2. The *cis*-diol system in the glycoside (25), which is more rapidly oxidised than the *trans*-diol system of (23), is able to complex effectively with phenylboronic acid in contrast to the *trans*-diol of (23). Also the *cis*-compound (24) can form a strong intramolecular hydrogen bond with oxygen in the *cis* adjacent dioxolan ring, but no intramolecular hydrogen bonding is apparent in compound (21).[14] These results establish the configurations assigned to compounds (21) and (24) and derivatives prepared from them.

The formation of the *xylo*-isomer (14) from diazomethane addition to the glycosulose (12) is interesting in view of the stereochemistry of addition of the Grignard reagent * and the similar formation of the ribose derivative by catalytic hydrogenation of the ulose (12) [15] and the formation of an *allo*-derivative in the reduction of the closely related 1,2 : 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (26),[16] all of which suggest that the isopropylidenedioxy-system on C-1 and C-2 offers more steric hindrance to addition than the alkyl function at C-4. The diazomethane molecule might be expected to be less sensitive to steric effects than a Grignard reagent, but preference for addition from the *endo*-side of the bicyclic system might indicate some kind of assistance by the oxygen at C-2 in the dioxolan ring to the addition of diazomethane from that side of the carbonyl group. Perhaps a favourable dipole interaction ensues,† and clearly the results of Horwitz *et al.*[11] indicate that changes in the polarity of the medium can affect the nature of the products. It is difficult to rationalise the preferential formation of the *xylo*-isomer (13) by diazomethane addition to the presumed intermediate, 6-*O*-benzoyl-4-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexopyranosid-3-ulose (27) since this requires attack from the much more hindered side of the carbonyl group with the compound in the anticipated preferred chair conformation shown. It is possible that the combined effect of the *cis*-fused dioxolan ring, together with the carbonyl group at C-3 which seeks an α-axial oxygen on C-2, forces the sugar to adopt a skew ($^0S_2$) form (28) in which diazomethane attack from the same side as the dioxolan ring may be rationalised as above. Axial attack by diazomethane on the carbonyl group in compound (1) would lead to compound (3) as the *minor* product. The more sterically favoured attack from the equatorial side could give an intermediate adduct which undergoes rearrangement in preference to epoxide formation and so the ring-expanded compound is the major product.

* Differences in the stereochemical course of addition of Grignard reagents and diazomethane to glycosiduloses have been noted previously.[5,6]

† In the transition state the nucleophile will carry some positive charge which can be partially neutralised by the adjacent oxygen on C-2 during *endo*-attack.

As suggested by a referee, it could equally well be that unfavourable 1,2- and 1,3-dipolar interactions ensue between the C–O⁻ bond of the developing dipolar intermediate and this adjacent oxygen during *exo*-attack.

[15] K. Oka and H. Wada, *Yakugaku Zasshi*, 1963, **83**, 890 (*Chem. Abs.*, 1964, **60**, 1825d).

[16] P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc.* (*C*), 1966, 1131.

EXPERIMENTAL

Methods and Materials.—I.r. spectra were recorded on a Perkin-Elmer 137 Infracord spectrophotometer; crystalline compounds were examined in potassium bromide discs and syrups as smears on such discs. High resolution i.r. spectra in the region 3650—3500 cm^{-1} were obtained with a Unicam SP 700 recording spectrometer, for 0·005M-solutions in carbon tetrachloride in 1 cm silica cells. N.m.r. spectra were recorded either on a Varian A-60 spectrometer (by courtesy of the School of Pharmacy, University of London) or on an HA-100 instrument (by courtesy of the Chemistry Department, Imperial College). Unless stated otherwise, all compounds were examined in deuteriochloroform with tetramethylsilane as internal reference.

Thin-layer chromatograms were prepared on 20 cm plates or microscope slides coated with silica gel G (Merck). The plates were activated either at 140° for 0·5 h [for solvents (*a*) and (*b*)] or at room temperature [for solvents (*c*) and (*d*)]. The following solvents were used (all ratios are v/v): (*a*) benzene–methanol (95 : 5); (*b*) benzene–methanol (98 : 2); (*c*) light petroleum (b.p. 60—80°)–ethyl acetate (3 : 2); (*d*) chloroform–ethyl acetate (7 : 3). Spots were located with anisaldehyde–sulphuric acid [reagent (i)].[17] Epoxides were detected with the Buchanan-Schwarz reagent [reagent (ii)].[18]

For paper chromatography Whatman no. 1 paper was used. Unless otherwise stated the solvent was butan-1-ol–ethanol–water (4 : 1 : 5) (organic phase). Spots were located with silver nitrate–sodium hydroxide.[19] Chromatograms run in solvent containing phenylboronic acid were first treated with hydrogen fluoride in acetone before spots were located according to the method of Britton.[20] G.l.c. was conducted on columns with Apiezon L as stationary phase on Celite (72—85 mesh), at a column temperature of 150°. Periodate oxidations were carried out by the spectrophotometric method of Ferrier and Aspinall.[21] Diazomethane in diethyl ether solution was prepared either by the method of Arndt [22] or by that of DeBoer and Backer.[23]

Methyl 1′,4-*Anhydro*-5,7-O-*benzylidene*-2,3-*dideoxy*-4-C-*hydroxymethyl*-α-D-ribo-*heptoside* (2).—Compound (1) [12] (55 g) in dry methanol (1·5 l) was treated with a solution of diazomethane (25 g) in ether (1 l) at room temperature, and the mixture was stored overnight. The solution was concentrated to 500 ml, a further quantity of diazomethane (5 g) in ether (200 ml) was added, and the mixture was stored for 24 h at room temperature. The yellow solution was concentrated and the residue was shown by t.l.c. [solvent (*a*), reagent (i)] to contain six components, two of which were epoxides (R_F 0·80 and 0·90) located by reagent (ii). Addition of propan-2-ol yielded crystals (23·4 g), the mother liquors yielding further crystals (2·4 g) on concentration. This material was shown by t.l.c. to be the epoxide with R_F 0·80 [solvent (*a*), reagents (i) and (ii)], with a trace of unchanged starting material (R_F 0·56). The crystals were then treated again with an excess of diazomethane as before, and the product was recrystallised from propan-2-ol to afford *compound* (2) (12·1 g, 20%), m.p. 154—154·5°, $[\alpha]_D^{20}$ +122° (*c* 0·8 in EtOAc) (Found: C, 65·9; H, 6·4; OMe, 10·8%; *M*, 296. $C_{16}H_{20}O_5$ requires C, 65·7; H, 6·9; OMe, 10·6%; *M*, 292).

The combined mother liquors from the propan-2-ol crystallisations were evaporated to yield a syrup which partially crystallised on storage for 1 week, the crystals being separated from the residual syrup on a porous tile. After several recrystallisation from aqueous methanol, *methyl* 1′,3-*anhydro*-4,6-O-*benzylidene*-2-*deoxy*-3-C-*hydroxymethyl*-α-D-arabino-*hexopyranoside* (3) was obtained (6·7 g, 11·5%), m.p. 116·5—117°, $[\alpha]_D$ +119° (*c* 0·5 in EtOAc), R_F 0·90 [solvent (*a*), reagent (i)] (Found: C, 64·7; H, 6·7; OMe, 11·95%; *M*, 278. $C_{15}H_{18}O_5$ requires C, 64·75; H, 6·5; OMe, 11·15%; *M*, 278), τ 2·60 (5H, Ph), 4·42 (1H, acetal H), 6·67 (3H, OMe), 5·12 (H-1), 7·6—8·4 (H-2 and 2′), 6·8 and 7·25; (CH_2 of epoxide), and 5·6—6·8 (4H). [Molecular weights of the epoxides (2) and (3) were obtained by titration of the epoxide function.[24]].

Methyl-5,7-O-*Benzylidene*-2,3-*dideoxy*-4-C-*methyl*-α-D-ribo-*heptoside* (4).—Compound (2) (5·7 g) was added to a stirred suspension of lithium aluminium hydride (6 g) in anhydrous ether (500 ml) and the mixture was heated under reflux for 8 h. Work-up in the usual way afforded *compound* (4) (3·8 g, 66%), m.p. 102—102·5° (from aqueous propan-2-ol), $[\alpha]_D^{20}$ +130° (*c* 0·4 in EtOH), R_F 0·52 [solvent (*b*), reagent (i)], $\nu_{max.}$ 3500 (OH), 760, and 710 (Ph) cm^{-1} (Found: C, 65·4; H, 7·4; OMe, 9·9. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5; OMe, 10·5%).

Methyl 2,3-*Dideoxy*-4-C-*methyl*-α-D-ribo-*heptoside* (5).—Compound (4) (1·34 g) in 96% ethanol (120 ml) was shaken with hydrogen over palladium–charcoal (5%) until uptake was complete. Removal of the catalyst and evaporation yielded a viscous syrup, purified by passage through a column of alumina in benzene–methanol (9 : 1); compound (5) was eluted with methanol as a syrup which slowly crystallised. Recrystallisation from ethyl acetate–light petroleum (b.p. 40—60°) gave *compound* (5) (76 mg, 8%), m.p. 90—90·5°, $[\alpha]_D$ +147° (*c* 1·1 in EtOH), no i.r. absorption at 710 or 760 cm^{-1} (Found: C, 51·9; H, 8·8; OMe, 14·8. $C_9H_{18}O_5$ requires C, 52·4; H, 8·8; OMe, 15·0%).

Methyl 4,6-O-*Benzylidene*-2-*deoxy*-3-C-*methyl*-α-D-arabino-*hexopyranoside* (11).—The epoxide (3) (1 g) was added as a solid to a stirred suspension of lithium aluminium hydride (1 g) in dry ether (200 ml) and the mixture was heated under reflux for 3 h. Excess of hydride was destroyed by careful addition of water and the ethereal solution was decanted. The solid residue was washed by decantation with more ether (3 × 100 ml). The combined ethereal extracts were dried, filtered, and evaporated; the residue (0·95 g) crystallised from light petroleum (b.p. 40—60°) as *needles* (0·82 g, 81%), m.p. 79—79·5°, $[\alpha]_D$ +122° (*c* 1 in EtOH), $\nu_{max.}$ 3300 and 3700 (OH), 3000, and 760 and 700 (Ph) cm^{-1} (Found: C, 63·8; H, 7·6; OMe, 10·3. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2; OMe, 11·0%). Examination of the hydroxy-stretching region of the i.r. spectrum of this compound under high resolution showed a strong absorption at 3590 cm^{-1} (OH).

Methyl 2-*Deoxy*-3-C-*methyl*-α-D-arabino-*hexopyranoside*.—The 4,6-*O*-benzylidene derivative (11) (1·38 g) of the title compound in 96% aqueous ethanol (150 ml) was shaken in hydrogen at room temperature over palladium–charcoal (5%). When hydrogen uptake ceased the mixture was

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filtered and the filtrate concentrated to a syrup which was extracted with methanol. Evaporation of the extract gave a solid which crystallised from chloroform–light petroleum (b.p. 40—60°) to give *methyl* 2-*deoxy*-3-C-*methyl*-α-D-arabino-*hexopyranoside* (0·74 g, 79%) as fine needles, m.p. 112—112·5°, $[\alpha]_D$ +140° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 3600 and 3400 (OH), and 3000 cm^{-1} (no absorption at 700 and 760 cm^{-1}) (Found: C, 49·7; H, 8·4; OMe, 15·6. $C_8H_{16}O_5$ requires C, 49·9; H, 8·4; OMe, 16·1%). This compound was oxidised by sodium periodate: 0·98 and 1·12 mol. equiv. of oxidant were consumed in 10 and 24 h, respectively.

5-O-*Benzoyl*-1,2-O-*isopropylidene*-α-D-erythro-*pentofuranos*-3-*ulose* (12).—5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose [25] was oxidised to 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose in 80% yield with ruthenium tetroxide.[16] Compound (12) was obtained as crystals from diethyl ether, m.p. 93·5—94·5°, $[\alpha]_D^{20}$ +135° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 1780 (ketone C=O(and 1720 (OBz) cm^{-1}; τ 3·87 (1H, H-1, $J_{1,2}$ 4·3 Hz), and 8·49 (3H) and 8·57 (3H) (CMe_2) (Found: C, 61·8; H, 5·7. Calc. for $C_{15}H_{16}O_6$: C, 61·6; H, 5·6%) (lit.,[15] m.p. 93—94·5°, $[\alpha]_D$ +134°). A gem-diol hydrate (m.p. 99—101°) was obtained on recrystallisation from aqueous tetrahydrofuran [$\nu_{max.}$ 3450 (OH) and 1720 cm^{-1} (OBz); no absorption at 1780 cm^{-1} (ketone C=O); τ 4·11 (1H, H-1, $J_{1,2}$ 4·1 Hz), 8·43 (3H) and 8·65 (3H) (CMe_2), and 6·27 (OH, disappears with D_2O)].

Treatment of the Ulose (12) *with Diazomethane*.—Compound (12) (50 g) in methanol (300 ml) was treated with diazomethane (14·2 g) in diethyl ether (120 ml) at room temperature and the mixture was stored overnight. More diazomethane (7 g) in diethyl ether was added, and after 4 h t.l.c. [solvent (*c*)] indicated that none of compound (12) remained. Two new products were detected (R_F 0·68 and 0·53), both giving a positive epoxide test. The solvent was removed to yield a viscous syrup which was separated on a silica column [solvent (*c*)] to afford 1′,3-*anhydro*-5-O-*benzoyl*-3-C-*hydroxymethyl*-1,2-O-*isopropylidene*-α-D-*xylofuranose* (14) (13 g), m.p. 44—45° [from light petroleum (b.p. 60—80°)], $[\alpha]_D^{20}$ +55° (*c* 1·0 in $CHCl_3$), R_F 0·68 [solvent (*c*)] (Found: C, 62·8; H, 6·3. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9%); τ 1·8—2·8 (5H, m, Ph), 3·90 (d, H-1, $J_{1,2}$ 4 Hz), 5·1—5·8 (4H, m, H-2, H-5, H-6), 6·79 (d) and 6·95 (d) (2H, epoxide, *J* 4·5 Hz), and 8·44 (s) and 8·69 (s) (6H, Me_2C); and 1′,3-*anhydro*-6-O-*benzoyl*-4-*deoxy*-3-C-*hydroxymethyl*-1,2-O-*isopropylidene*-α-D-xylo-*hexopyranose* (13) (35·6 g), m.p. 76—77° [from light petroleum (b.p. 60—80°)], $[\alpha]_D^{20}$ +31° (*c* 1·0 in $CHCl_3$) (Found: C, 63·7; H, 6·3%; *M*, 318·9, 321·7. $C_{17}H_{20}O_6$ requires C, 63·7; H, 6·3%; *M*, 320·2).

4-*Deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-xylo-*hexopyranose* (15).—1′,3-Anhydro-6-*O*-benzoyl-4-deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (2·5 g) in dry tetrahydrofuran (50 ml) was added to a stirred suspension of lithium aluminium hydride (0·7 g) in tetrahydrofuran (150 ml) and the mixture was heated under reflux until reaction was complete (2 h). Work-up in normal manner yielded a syrupy product comprised of two components [as indicated by t.l.c. (solvent (*c*)], which were separated on a column of silica gel with solvent (*c*). The main fraction, eluted first, was crystallised from light petroleum (b.p. 40—60°) to give *compound* (15) (1·2 g, 70%), m.p. 84—85°, $[\alpha]_D^{20}$ −15° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3500 (OH) [no peak at 710 cm^{-1} (Ph)] (Found: C, 54·9; H, 8·5. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%). Treatment of this substance (2 g) in dry pyridine (20 ml) with toluene-*p*-sulphonyl chloride (1·9 g, 1·1 mol. equiv.) in chloroform at 0° for 12 h gave 4-*deoxy*-1,2-*O*-*isopropylidene*-3-C-*methyl*-6-O-p-*tolylsulphonyl*-α-D-xylo-*hexopyranose* (17) (85%), m.p. 95—96·5° [from light petroleum (b.p. 40—60°)], $[\alpha]_D^{20}$ −44° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3500 (OH), 1160 (SO), and 840 and 780 (C_6H_4) cm^{-1} (Found: C, 54·7; H, 6·6; S, 8·25. $C_{17}H_{24}O_7S$ requires C, 54·8; H, 6·5; S, 8·6%).

Treatment of compound (15) (1 g) in absolute methanol (20 ml) with Amberlite resin (IR-120; H^+) at room temperature for several hours followed by removal of the resin and solvent afforded a syrupy product, $[\alpha]_D^{20}$ +29·2° (*c* 1 in $CHCl_3$), non-reducing towards Fehling's solution and considered to be methyl 4-deoxy-3-*C*-methyl-αβ-D-xylopyranoside (16). Oxidation with sodium periodate at 35°, followed spectrophotometrically,[21] led to the slow consumption of 1·03 mol. equiv. of oxidant in 42 h without production of formaldehyde.

3,6-*Anhydro*-4-*deoxy*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-xylo-*hexopyranose* (18).—The tosyl ester (17) (1 g) in dry methanol (10 ml) was treated with 4% sodium methoxide in methanol (20 ml) for 24 h at room temperature. The solution was neutralised with 2N-hydrochloric acid and extracted with dichloromethane (3 × 60 ml). The dried extract was concentrated to a syrup which crystallised on storage. Recrystallisation from aqueous methanol (1 : 1) gave the *anhydride* (0·46 g, 85%), m.p. 66—67°, $[\alpha]_D^{20}$ +57·7° (*c* 1 in $CHCl_3$) [no i.r. absorption at 3500 cm^{-1} (OH)] (Found: C, 60·4; H, 7·9. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%), τ 4·30 (d, H-1, $J_{1,2}$ 4·5 Hz), 5·7—6·3 (4H, m, H-2, H-5, H-6), 7·6—8·3 (m, H-4), and 8·43 (s), 8·63 (s), and 8·72 (s) (each 3H, CMe).

1,2-O-*Isopropylidene*-3-C-*methyl*-α-D-*xylofuranose* (19).—The epoxide (14) (1 g) was reduced with lithium aluminium hydride as described for the preparation of compound (4) except that tetrahydrofuran was used instead of diethyl ether (this modification led to improved yield). After heating under reflux for 2·5 h the mixture contained two components (g.l.c. analysis). By crystallisation and recrystallisation from light petroleum (b.p. 40—60°), *compound* (19) (65%) was obtained with m.p. 67—68°, $[\alpha]_D^{20}$ +27° (*c* 1·8 in $CHCl_3$), $\nu_{max.}$ 3400 (OH) [no peaks at 710 or 1600 (Ph)] cm^{-1} (Found: C, 52·9; H, 8·0. $C_9H_{16}O_5$ requires C, 52·9; H, 7·9%).

This substance (1·5 g) readily afforded the 5-O-*tosyl derivative* (20) (70%), m.p. 154—155° (decomp.) (from ethanol), $[\alpha]_D^{20}$ +30° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 3500 (OH), 1170 (SO), and 1600 and 775 (C_6H_4) cm^{-1} (Found: C, 53·5; H, 6·3; S, 9·1. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·2; S, 8·9%). The 5-benzoate (21) had m.p. 112—113°, $[\alpha]_D^{20}$ +50° ($CHCl_3$).

Treatment of compound (19) (0·5 g) in methanol (15 ml) with Amberlite resin (IR-120; H^+) at 35° for 4 h followed by filtration and evaporation yielded a syrup, reducing to Fehling's solution, which was heated with dry methanol (15 ml) containing hydrogen chloride (0·08%), at 50° for 6 h. Neutralisation of the mixture, followed by the usual work-up, afforded a syrup, considered to be methyl 3-*C*-methyl-αβ-D-xylofuranoside (23). This material consumed 1·02 mol. equiv. of sodium periodate at 35° over 42 h.

3,5-*Anhydro*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*xylofuranose* (22).—The tosylate (20) (0·5 g) was treated with 4% sodium methoxide in methanol (20 ml) as described for the preparation of compound (18) to yield the 3,5-*anhydride* (22) (75%) as a syrup, b.p. 160° (bath temp.) at 0·1 mmHg,

[25] P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, 1933, **102**, 317.

$[\alpha]_D^{20}$ +19° (*c* 0·5 in $CHCl_3$) [very weak absorption at 3500 (OH), no peak at 1600 (C_6H_4Me) cm^{-1}] (Found: C, 58·0; H, 7·6. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%).

5-O-*Benzoyl*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*ribofuranose* (24).—5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (12) (5 g) in dry tetrahydrofuran (200 ml) was added dropwise to a stirred solution of methylmagnesium iodide [from methyl iodide (4·2 ml) and magnesium (5 g)] in diethyl ether (150 ml). The mixture was stirred at room temperature for 2 h and then heated under reflux for 1 h. Work-up in the usual way yielded a product shown by t.l.c. [solvent (*d*)] to contain two components. The major component (higher R_F value) was isolated after column chromatography on silica gel with solvent (*d*) to give 5-O-*benzoyl*-1,2-O-*isopropylidene*-3-C-*methyl*-α-D-*ribofuranose* (70%) m.p. 104—105° [from light petroleum (b.p. 60—80°)], $[\alpha]_D^{20}$ +35° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 3500 (OH), 1740 (CO), and 1620 and 715 (Ph) cm^{-1} (Found: C, 62·2; H, 6·4. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%), τ 1·8—2·7 (5H, m, Ph), 4·19 (d, H-1, $J_{1,2}$ 3·8 Hz), 5·62 (q) and 5·41 (q) (H-5,-5′, $J_{5,5'}$ 11·0, $J_{4,5}$ 3·6, $J_{4,5'}$ 7·2 Hz), 5·86 (d, H-2), 5·88 (q, H-4), 7·22 (s, OH), and 8·41 (s), 8·64 (s), and 8·75 (s) (3 × CMe), identical with an authentic sample kindly provided by Dr. E. Walton (Merck, Sharpe and Dohme Research Laboratory, Rahway, New Jersey).

On treatment of this compound (0·5 g) in methanol with Amberlite resin (IR-120; H^+) at 35° for 8 h followed by the usual work-up, a syrup was obtained which then was treated with methanol (15 ml) containing hydrogen chloride (0·08%) as described for the preparation of compound (23). The syrupy product, $[\alpha]_D^{20}$ +27° (*c* 1·1 in $CHCl_3$), is considered to be methyl 3-*C*-methyl-αβ-D-ribofuranoside (25): it consumed 1·04 mol. equiv. of sodium periodate in 0·5 h at room temperature, and after this period there was no further consumption of oxidant over 24 h.

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