Displacement Reactions of Acyclic Carbohydrate Derivatives. Part II.[1] A 1,4-Methoxyl Group Migration following Acetal Participation: 4-*O*-Methyl-L-lyxose[2]

By **N. A. Hughes** and **P. R. H. Speakman**, Department of Organic Chemistry, The University, Newcastle upon Tyne 1

The benzoate displacement reaction on 2,3,5-tri-*O*-benzyl-4-*O*-toluene-*p*-sulphonyl-D-ribose dimethyl acetal gave not the expected 4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-L-lyxose dimethyl acetal but the isomeric 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-4-*O*-methyl-L-lyxose methyl hemiacetal as a consequence of methoxyl group participation and migration. The structure of the product was determined by conversion into the known 4-*O*-methyl-L-lyxitol (2-*O*-methyl-L-arabinitol) and into 4-*O*-methyl-L-lyxose. 4-*O*-Methyl-D-lyxose has been synthesised.

THE benzoate displacement of sulphonate ester groups has found wide application in carbohydrate chemistry. Displacement may occur with [3,4] or without [3,5,6] participation from a neighbouring carboxylic ester group, and variations, *e.g.*, olefin [7,8] and epoxide [8] formation, have been reported. In our own study of benzoate displacement reactions we have observed another variation, methoxyl-group migration, in the reaction of the acyclic 2,3,5-tri-*O*-benzyl-4-*O*-toluene-*p*-sulphonyl-D-ribose dimethyl acetal (VIII) with benzoate ions.

Derivatives of D-ribose bearing a free 4-hydroxyl group are not numerous. The simplest approach to such compounds is to convert a suitably protected D-ribofuranose into an acyclic derivative. A similar method has recently been employed in the D-arabinose series.[9] Treatment of the known [10] 2,3,5-tri-*O*-benzyl-D-ribofuranose (I), which in our hands was obtained in crystalline form, with ethanethiol in dioxan containing hydrogen chloride gave the dithioacetal (II). Acetylation gave the acetate (III) which with methanol and mercuric chloride was converted into the acetal (IV). Alkaline removal of the acetyl group gave the alcohol (V) which was too unstable for characterisation. Slowly, or more rapidly when chromatographed on silica gel, it was converted into a product free of hydroxyl groups, probably the furanoside (VI). Acetylation of the alcohol (V) regenerated the acetate (IV), and the alcohol (V) was further characterised as the benzoate (VII). With toluene-*p*-sulphonyl chloride in pyridine, the alcohol (V) gave the required sulphonate (VIII).

Treatment of the sulphonate (VIII) with sodium benzoate in dimethylformamide gave unsatisfactory results but tetra-n-butylammonium benzoate in *N*-methylpyrrolidone [6] gave good yields of a product which had a satisfactory analysis on the assumption that the sulphonate group of the ester (VIII) had been replaced by a benzoate group. However, the product was not the expected benzoate (IX) but the isomeric hemiacetal benzoate (X). Two diastereoisomers are possible for this structure, owing to the asymmetry at C-1, and the product might be a mixture of the two.

The structure (X) was proved in the following manner. Methanolysis of the hemiacetal benzoate (X) gave the acetal (XI). This was readily hydrolysed by dilute acid to an aldehyde which, on borohydride reduction, gave

[1] N. A. Hughes and R. Robson, *J. Chem. Soc.* (*C*), 1966, 2366, is considered to be Part I of the Series.
[2] Preliminary communication, N. A. Hughes and P. R. H. Speakman, *Chem. Comm.*, 1965, 199.
[3] M. A. Bukhari, A. B. Foster, J. Lehmann, M. H. Randall, and J. M. Webber, *J. Chem. Soc.*, 1963, 4167.
[4] E. J. Reist, L. V. Fischer, and D. E. Gueffroy, *J. Org. Chem.*, 1966, **31**, 226.
[5] B. R. Baker, E. J. Reist, and R. R. Spencer, *J. Org. Chem.*, 1959, **24**, 1618.
[6] N. A. Hughes and P. R. H. Speakman, *J. Chem. Soc.*, 1965, 2236.
[7] M. A. Bukhari, A. B. Foster, and J. M. Webber, *J. Chem. Soc.*, 1964, 2514.
[8] S. J. Angyal and T. S. Stewart, *Proc. Chem. Soc.*, 1964, 331.
[9] H. G. Fletcher and H. W. Diehl, *J. Org. Chem.*, 1965, **30**, 2321.
[10] R. Barker and H. G. Fletcher, *J. Org. Chem.*, 1961, **26**, 4605.

the primary alcohol (XII). Removal of the benzyl groups by hydrogenolysis over a palladium catalyst yielded crystalline 2-*O*-methyl-L-arabinitol (4-*O*-methyl-L-lyxitol) (XIII); its physical constants indicated that it was the enantiomer of the known [11] 2-*O*-methyl-D-arabinitol. Confirmation of the structure (XIII) was obtained by comparison with an authentic sample synthesised as described [11] for the D-form. Further proof of the structure of the benzoate (X) was obtained by hydrogenolysis of the methanolysis product (XI). The resulting acetal (XIV) readily underwent conversion into the glycoside (XV) during the reaction or subsequent distillation. The glycoside (XV) consumed the expected molar equivalent of periodate and on hydrolysis gave 4-*O*-methyl-L-lyxose (XVI) which was characterised as the crystalline diethyl dithioacetal. For comparison, 4-*O*-methyl-D-lyxose (XX) was prepared.

Methylation of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside (XVII) [12] with dimethyl sulphate gave the methyl ether (XVIII), which on mild acid hydrolysis lost the ketal group to give the glycoside (XIX). More vigorous conditions led to the free sugar (XX) which gave a crystalline diethyl dithioacetal enantiomeric with that prepared from the sugar (XV). A similar synthesis of 4-*O*-methyl-D-lyxose from ethyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside was recently reported.[13]

The unexpected course of the benzoate displacement reaction is evidently the result of an intramolecular displacement by a methoxyl group in the sulphonate (VIII) to give the cyclic oxonium ion (XXI) which can be

[11] J. C. Sowden, M. L. Oftedahl, and A. Kirkland, *J. Org. Chem.*, 1962, **27**, 1791.
[12] P. W. Kent and P. F. V. Ward, *J. Chem. Soc.*, 1953, 416.
[13] J. Piotrovsky, J. P. Verheijden, and P. J. Stoffyn, *Bull. Soc. chim. belges*, 1964, **73**, 969.

opened up by a mesomeric effect from the second methoxyl group to give the new ion (XXII). This then reacts with the benzoate ions present to give the hemiacetal benzoate (X); the possibility of direct attack by a benzoate ion on the cyclic ion (XXI) also exists. Winstein *et al.* have shown that methoxyl group participation is particularly favourable when the cyclic oxonium ion is five-membered.[14] Recently it has been shown[15] that chloride ions are liberated more rapidly by 4-chloro-1,1-diethoxybutane in ethylene glycol containing potassium hydroxide than by 5-chloro-1,1-diethoxypentane. The intermediacy of a cyclic oxonium ion resulting from ethoxyl participation in the butane case was suggested. However, in contrast to the present result, the product was entirely 4,4-diethoxybutan-1-ol; no 1,4-diethoxybutan-1-ol or 4-ethoxybutanal was detected.

Other cases of methoxyl group participation in the carbohydrate field are known. 1,3,4,6-Tetra-*O*-acetyl-2-*O*-methyl-D-glucopyranose was obtained in small yield in the brominolysis of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside in acetic acid.[16] More recently, methyl 5-*O*-bromobenzenesulphonyl-6-deoxy-2,3-*O*-isopropylidene-β-L-allofuranoside gave 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methyl-D-talofuranose on treatment with sodium hydroxide in aqueous dioxan.[17] It is noteworthy that in these examples, and in the present case, the participating methoxyl group undergoing migration is part of an acetal group. No participation or migration was observed in the benzoate displacement reactions on 1,2:5,6-di-*O*-isopropylidene-3(or 4)-*O*-methanesulphonyl-4(or 3)-*O*-methyl-D-mannitol. Participation by benzyloxy groups by way of favourable five-membered cyclic oxonium ions has been demonstrated in solvolyses of pentitol sulphonates.[18]

Attempts to prepare a toluene-*p*-sulphonate of the dithioacetal (II) were unsuccessful and intractable products were obtained. The fact that the dithioacetal (II) readily gave a benzoate suggests that the failure to obtain a sulphonate was not due to steric hindrance. It seems likely that a sulphonate was produced which decomposed too rapidly for it to be isolated. The decomposition was probably initiated by an intramolecular displacement from a thioethyl group to give a sulphur analogue of the cyclic oxonium ion (XXI). Experiments with 5-*O*-toluene-*p*-sulphonyl-L-arabinose diethyl dithioacetal, which is converted in neutral aqueous conditions into ethyl 1,5-dideoxy-5-ethylthio-1-mercapto-αβ-L-arabinofuranoside, probably *via* a cyclic sulphonium ion, lend weight to this suggestion.[1]

EXPERIMENTAL

Hydrogenolyses were performed at room temperature and pressure. Silica gel (Hopkin and Williams, M.F.C. grade) and alumina (Savory and Moore) were used for column chromatography. Silica gel (Merck, G grade) were used for thin-layer chromatography (t.l.c.). The solvent system, butanol–water (86 : 14 v/v), was used with Whatman No. 1 paper for paper chromatography. Reducing sugars were detected with aniline phthalate[19] or silver nitrate.[20] Light petroleum had b. p. 60—80°.

2,3,5-*Tri*-O-*benzyl*-D-*ribofuranose* (I).—Prepared as described by Barker and Fletcher,[10] the syrupy sugar (I) crystallised after some time. Recrystallised from large volumes of light petroleum it had m. p. 50—51°, $[\alpha]_D$ +42° (*c* 1 in dioxan) (lit.,[10] $[\alpha]_D$ +37°) (Found: C, 74·0; H, 6·5. Calc. for $C_{26}H_{28}O_5$: C, 74·3; H, 6·7%).

2,3,5-*Tri*-O-*benzyl*-D-*ribose Diethyl Dithioacetal* (II).—The sugar (I) (25 g.) was dissolved in dioxan (60 ml.) containing hydrogen chloride (8·6 g.) and ethanethiol (25 ml.). After 21 hr. at room temperature chloroform and water were added and the chloroform extract was washed successively with dilute sodium hydrogen carbonate and water. Chromatography on alumina (650 g.) of the syrup (32·3 g.) obtained from the chloroform and elution first with benzene, which removed impurities (2·4 g.), and then with benzene–ether (1 : 1) gave the *dithioacetal* (II) as a pale yellow syrup (23·2 g.), $[\alpha]_D$ +22° (*c* 0·9 in dioxan) (Found: C, 67·9; H, 7·3; S, 12·5. $C_{30}H_{38}O_4S_2$ requires C, 68·4; H, 7·2; S, 12·2%).

4-*O*-*Acetyl*-2,3,5-*tri*-O-*benzyl*-D-*ribose Diethyl Dithioacetal* (III).—The dithioacetal (II) (21 g.) in pyridine (140 ml.) was treated with acetic anhydride (22 ml.) for 16 hr. at room temperature. Isolation using chloroform gave the *acetate* (III) as a syrup (22·3 g.), $\nu_{max.}$ 1740 cm.$^{-1}$ (OAc), $[\alpha]_D$ +27° (*c* 1·0 in dioxan) (Found: C, 67·3; H, 7·2; S, 11·6. $C_{32}H_{40}O_5S_2$ requires C, 67·6; H, 7·0; S, 11·3%).

4-O-*Acetyl*-2,3,5-*tri*-O-*benzyl*-D-*ribose Dimethyl Acetal* (IV).—The acetate (III) (22·2 g.) in methanol (300 ml.) was stirred with cadmium carbonate (40 g.) while a solution of mercuric chloride (64 g.) in methanol (200 ml.) was added. The temperature was maintained at 60° for 3 hr. during which time more cadmium carbonate (12 g.) was added. The solution was filtered into water (1 l.) and extracted with chloroform (3 × 200 ml.). The product was thus obtained as a syrup (19·7 g.). Chromatography of a portion (50 mg.) on alumina (5 g.) and elution with benzene–ether (19 : 1) gave the *acetal* (IV) (40 mg.), $\nu_{max.}$ 1740 cm.$^{-1}$ (OAc), $[\alpha]_D$ +25° (*c* 1·1 in dioxan) (Found: C, 70·4; H, 6·9. $C_{30}H_{36}O_7$ requires C, 70·9; H, 7·1%).

2,3,5-*Tri*-O-*benzyl*-D-*ribose Dimethyl Acetal* (V).—The acetal (IV) (19·4 g.) was dissolved in 0·03N-sodium methoxide (120 ml.). After 48 hr. at 4° the solution was neutralised with carbon dioxide, and water and chloroform were added. T.l.c. of the product (16·5 g.) from the chloroform extract indicated that it was largely the desired acetal (V) contaminated with a little methyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside (VI). Chromatography of a portion (150 mg.) of the product on alumina (4 g.) and elution with benzene gave the furanoside (VI) (20 mg.) and elution with ether gave the acetal (V) (130 mg.), $\nu_{max.}$ 3450 cm.$^{-1}$ (OH). During storage the acetal (V) slowly changed into the furanoside (VI). The acetal (V) on acetylation re-formed the

[14] S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, 1958, **3**, 1.
[15] J. P. Ward, *Tetrahedron Letters*, 1965, 3905.
[16] R. U. Lemieux and B. Fraser-Reid, *Canad. J. Chem.*, 1964, **42**, 539.
[17] C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and F. Sirokman, *J. Amer. Chem. Soc.*, 1966, **88**, 2073.
[18] C. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, 1965, **30**, 2020.
[19] S. M. Partridge, *Nature*, 1949, **164**, 443.
[20] W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, 1950, **166**, 444.

acetate (IV) and on benzoylation gave a syrupy *benzoate* (VII), $\nu_{max.}$ 1725 cm.$^{-1}$ (OBz), $[\alpha]_D$ +20° (*c* 0·9 in dioxan) (Found: C, 73·5; H, 6·7. $C_{35}H_{38}O_7$ requires C, 73·7; H, 6·7%).

2,3,5-*Tri*-O-*benzyl*-4-O-*toluene*-p-*sulphonyl*-D-*ribose Dimethyl Acetal* (VIII).—Toluene-*p*-sulphonyl chloride (30·7 g.) was slowly added to the acetal (V) (15 g.) in pyridine (100 ml.) at 0°. After 3 days at 20° the product was isolated, in the usual manner with chloroform, as a red syrup (20·3 g.). Chromatography on silica and elution with benzene–ether (19 : 1) gave the *sulphonate* (VIII) as a chromatographically homogeneous syrup, $\nu_{max.}$ 1188 and 1175 cm.$^{-1}$ (OTs), $[\alpha]_D$ +19·4° (*c* 2·0 in $CHCl_3$) (Found: C, 67·3; H, 6·6; S, 4·9. $C_{35}H_{40}O_8S$ requires C, 67·7; H, 6·5; S, 5·1%).

1-O-*Benzoyl*-2,3,5-*tri*-O-*benzyl*-4-O-*methyl*-L-*lyxose Methyl Hemiacetal* (X).—The sulphonate (VIII) (2·2 g.) in *N*-methylpyrrolidone (20 ml.) containing tetra-n-butylammonium benzoate (5 g.) was kept at 110° for 16 hr. T.l.c. revealed the presence of only one product. The solution was concentrated to a small volume and then washed through silica (100 g.) with ether (300 ml.). The eluate was concentrated and washed through alumina (30 g.) with more ether (100 ml.). The resultant ether solution, now free of *N*-methylpyrrolidone and benzoic acid, was evaporated to yield a product (1·6 g.) which was chromatographed on silica (60 g.). Elution with benzene–ether (19 : 1) gave the syrupy *benzoate* (X) (1·43 g.), $\nu_{max.}$ 1720 cm.$^{-1}$ (OBz), $[\alpha]_D$ +3·8° (*c* 1·3 in dioxan) (Found: C, 73·5; H, 6·8. $C_{35}H_{38}O_7$ requires C, 73·7; H, 6·7%).

2,3,5-*Tri*-O-*benzyl*-4-O-*methyl*-L-*lyxose Dimethyl Acetal* (XI).—The benzoate (X) (1·25 g.) was kept in methanol (30 ml.) containing hydrogen chloride (1·5 g.) for 92 hr. at 20°. Water and chloroform were added and the chloroform extract gave a syrup (1·2 g.) which was chromatographed on silica (40 g.). Benzene–ether (49 : 1) eluted methyl benzoate (0·22 g.), and benzene–ether (19 : 1) gave the *acetal* (XI) (0·86 g.) as a syrup (Found: C, 72·3; H, 7·4. $C_{29}H_{36}O_6$ requires C, 72·5; H, 7·5%).

2,3,5-*Tri*-O-*benzyl*-4-O-*methyl*-L-*lyxitol* (XII).—Hydrolysis of the acetal (XI) (235 mg.) in acetone (8 ml.) and 2N-sulphuric acid (2 ml.) was complete after 24 hr. at 37°. Isolation using chloroform and water gave a product (214 mg.) exhibiting the expected aldehyde absorption (1745 cm.$^{-1}$). This was dissolved in methanol (10 ml.) containing sodium borohydride (50 mg.), and the solution was kept overnight before being neutralised with acetic acid. The crude product (188 mg.) was isolated with chloroform. Chromatography on silica (10 g.) and elution with benzene–ether (95 : 5) removed by-products (40 mg.), and benzene–ether (4 : 1) gave the *lyxitol* (XII) (140 mg.) as a syrup (Found: C, 74·1; H, 7·6. $C_{27}H_{32}O_5$ requires C, 74·3; H, 7·3%).

2-O-*Methyl*-L-*arabinitol* (4-O-*Methyl*-L-*lyxitol*) (XIII).—(a) *From methyl* 3,4-O-*isopropylidene*-β-L-*arabinopyranoside*. An authentic sample of 2-*O*-methyl-L-arabinitol was synthesised essentially in the manner described for the D-form. Crystallised from ethanol, the *arabinitol* (XIII) had m. p. 98—99°, $[\alpha]_D$ +10·4° (*c* 1·9 in MeOH) (Found: C, 43·3; H, 8·1. $C_6H_{14}O_5$ requires C, 43·4; H, 8·4%) (lit.,[11] m. p. 98—99°, $[\alpha]_D$ −11° for 2-*O*-methyl-D-arabinitol).

(b) *From the benzyl ether* (XII). The ether (XII) (117 mg.) was hydrogenolysed in ethanol (5 ml.) over a palladium catalyst [from PdO_2 (0·1 g.)]. Crystallisation of the syrupy product (46 mg.) from ethanol–ether gave the arabinitol (XIII), m. p. and mixed m. p. 97°, $[\alpha]_D$ +9·6° (*c* 0·8 in MeOH).

Catalytic Hydrogenolysis of 2,3,5-*Tri*-O-*benzyl*-4-O-*methyl*-L-*lyxose Dimethyl Acetal* (XI).—The acetal (XI) (0·58 g.) was hydrogenolysed in methanol (20 ml.) over palladium [from PdO_2 (0·5 g.)] overnight at 20°, and yielded a syrup (165 mg.). Chromatography of the syrup on Dowex-1 (hydroxide form) ion-exchange resin (40 ml.) and elution with water (10-ml. fractions) gave chromatographically homogeneous material (146 mg.) in fractions 4—6. Distillation at 80—90°/0·5 mm. gave *methyl* 4-O-*methyl*-L-*lyxopyranoside* (XV) chromatographically indistinguishable from the α-D-isomer (XIX) (Found: C, 47·6; H, 8·3. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9%) (periodate uptake: 1·02 moles/mole).

4-O-*Methyl*-L-*lyxose* (XVI).—The lyxoside (XV) (0·29 g.) was hydrolysed in 0·4N-sulphuric acid (10 ml.) at 100° for 2 hr. After neutralisation with Dowex-2 (carbonate form) ion-exchange resin and evaporation, the solution yielded the syrupy sugar (XVI) (0·22 g.), R_{lyxose} 2·2. The sugar (XVI) (125 mg.) was shaken with concentrated hydrochloric acid (0·1 ml.) and ethanethiol (0·4 ml.) for 30 min. at 0°. Addition of water and neutralisation and evaporation as above gave a residue (130 mg.) which was chromatographed on cellulose powder (25 × 1·8 cm.) and eluted with methyl ethyl ketone saturated with water. 4-O-*Methyl*-L-*lyxose diethyl dithioacetal* (98 mg.) was eluted in the early fractions and had m. p. 73—74° (from ether–light petroleum), $[\alpha]_D$ −24° (*c* 0·8 in MeOH) (Found: C, 44·1; H, 7·9; S, 23·5. $C_{10}H_{22}O_4S$ requires C, 44·4; H, 8·15; S, 23·7%).

Methyl 2,3-O-*Isopropylidene*-4-O-*methyl*-α-D-*lyxopyranoside* (XVIII).—A solution of methyl 2,3-*O*-isopropylidene-α-D-lyxopyranoside (XVII)[12] (1·43 g.) in acetone (20 ml.) containing crushed sodium hydroxide (1·1 g.) and dimethyl sulphate (1·5 ml.) was stirred and heated under reflux for 6 hr. Isolation with chloroform yielded a syrup (1·45 g.) which was chromatographed on silica (50 g.). Non-carbohydrate material (0·2 g.) was eluted with benzene, and benzene–ether (85 : 15) gave the *ether* (XVIII) (1·14 g.), b. p. 65°/0·5 mm., $[\alpha]_D$ +60° (*c* 0·7 in $CHCl_3$) (Found: C, 54·6; H, 8·3. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%).

Methyl 4-O-*Methyl*-α-D-*lyxopyranoside* (XIX).—Hydrolysis in acetic acid–water (4 : 1) for 5 min. at 100° removed the ketal group from the ether (XVIII) (0·48 g.). Chromatography of the product on silica and elution with ether–methanol (19 : 1) gave a little starting material (25 mg.) and then the product (XIX) (0·36 g.) which was further chromatographed on Dowex-1 (hydroxide form) ion-exchange resin. The *lyxoside* (XIX), which failed to crystallise, had $[\alpha]_D$ +69° (*c* 0·8 in MeOH) (Found: C, 47·3; H, 7·6. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9%) (periodate uptake: 1·01 moles/mole).

4-O-*Methyl*-D-*lyxose* (XX).—The glycoside (XIX) (0·17 g.) in N-sulphuric acid was kept at 100° for 4 hr. After neutralisation with Dowex-2 (carbonate form) ion-exchange resin and evaporation, the solution yielded the syrupy sugar (XX), R_{lyxose} 2·2. The *diethyl dithioacetal*, synthesised as described for the L-form, had m. p. 74—75° (from ether–light petroleum), $[\alpha]_D$ +25·7° (*c* 1·15 in MeOH), and its i.r. spectrum was indistinguishable from that of the L-form (Found: C, 44·6; H, 8·0; S, 23·9. $C_{10}H_{22}O_4S_2$ requires C, 44·4; H, 8·15; S, 23·7%).

One of us (P. R. H. S.) thanks the S.R.C. for a Research Studentship.

[6/1616 *Received, December 20th,* 1966]