NUCLEOPHILIC DISPLACEMENT REACTIONS IN CARBOHYDRATES

PART XVII[1]. A SYNTHESIS OF 3,6-ACETYLEPIMINO-3,6-DIDEOXY-1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE AND A CORRELATION OF STRUCTURE

J. S. BRIMACOMBE AND A. M. MOFTI
The Chemistry Department, The University, Dundee DD1 4HN (Great Britain)
(Received September 21st, 1970; accepted for publication, October 20th, 1970)

ABSTRACT

An unequivocal synthesis of the title compound was achieved by means of intramolecular cyclization of 6-amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose (**7**) and *N*-acetylation of the resulting epimino derivative. The derived methanesulphonate **9** readily underwent a displacement reaction with sodium benzoate in *N*,*N*-dimethylformamide to give 3,6-acetylepimino-5-*O*-benzoyl-3,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**10**), whose structure was correlated with that of a product previously obtained from the solvolysis of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-5,6-di-*O*-methanesulphonyl-α-D-glucofuranose (**1**).

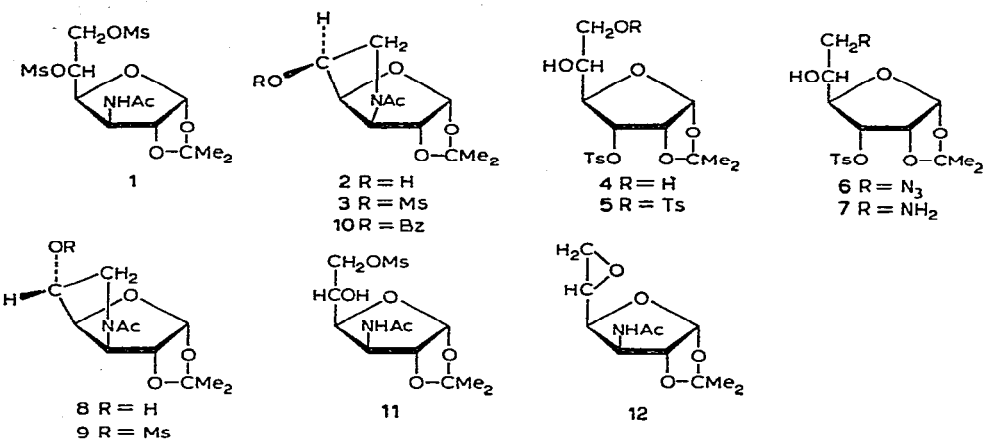
INTRODUCTION

In an earlier paper[2], we reported that the solvolysis of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-5,6-di-*O*-methanesulphonyl-α-D-glucofuranose (**1**) in buffered, 95% 2-methoxyethanol gave a product tentatively identified as 3,6-acetylepimino-3,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**2**). The gross features of structure of this compound were revealed by i.r. and n.m.r. spectroscopy, but we were unable to satisfy ourselves completely on the stereochemistry at C-5. The L-*ido* configuration was assigned[2] on the assumption that the 3-acetamido group participated[3] in the solvolysis of the C-5 sulphonic ester group, thereby causing inversion of configuration at this centre. The unreactivity of the derived methanesulphonate **3** towards bimolecular displacement was indicative[4] of the *exo* configuration of the sulphonic ester group with respect to the oxa-azabicyclo[3.3.0]octane ring-system, again implying the L-*ido* configuration for **2**.

DISCUSSION

In seeking to put the stereochemistry of **2** beyond dispute, a number of possible routes to related 3,6-acetylepimino derivatives were examined. One method was reported[5] during the course of our investigation, and this involved the cyclization of 3-azido-1,2-*O*-cyclohexylidene-3-deoxy-5,6-di-*O*-methanesulphonyl-α-D-glucofuranose by use of sodium iodide and zinc dust in boiling, aqueous *N*,*N*-dimethylformamide. Our procedure differs from this, since it involved the cyclization of the key

intermediate **7**; in this respect, it is analogous to the procedure recently described by Heap and Owen[6] for the synthesis of a related cyclic sulphide.



6-Amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose (**7**) was prepared by means of selective tosylation of the monosulphonate **4** to give the 3,6-disulphonate **5**, which, on heating with sodium azide in *N*,*N*-dimethylformamide at 65°, afforded a crystalline product presumed to be 6-azido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose (**6**). This assignment is supported by the fact that the primary sulphonic ester group of 1,2-*O*-isopropylidene-3,5-di-*O*-toluene-*p*-sulphonyl-α-D-ribofuranose is more reactive than the secondary sulphonic ester group under comparable conditions[7]. Hydrogenolysis of the azide **6** over palladised calcium carbonate yielded the required amine **7**, which was smoothly cyclized by heating in ethanol in the presence of sodium acetate to give, after *N*-acetylation, 3,6-acetylepimino-3,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**8**).

The tricyclic structure of **8** was clearly indicated by the i.r. spectrum, which showed no absorptions attributable to an NH group. Further, the n.m.r. spectrum of **8** (Fig. 1) was closely similar, in many respects, to that[2] of the other *N*-acetylepimine derivative **2**, and revealed the presence of two rotamers in solution, arising from hindered internal rotation about the N–$COCH_3$ bond[8]. In view of the method of preparation, the stereochemistry of **8** is indisputable. The physical properties of the *N*-acetylepimines **2** (Ref. 2) and **8** were distinct, thus verifying our original assignment of configuration to the former.

This evidence is reinforced by the following conversion. The sulphonic ester group of the methanesulphonate **9** (derived from the D-*gluco* epimine **8**) has an *endo* configuration with respect to the oxa-azabicyclo[3.3.0]octane ring-system and, thus, would be expected[4] to undergo S_N2 displacements without difficulty. A good analogy is provided by the ease with which such displacements are accomplished[9] with 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose. Replacement of the sulphonic ester group occurred on treatment of **9** with sodium benzoate

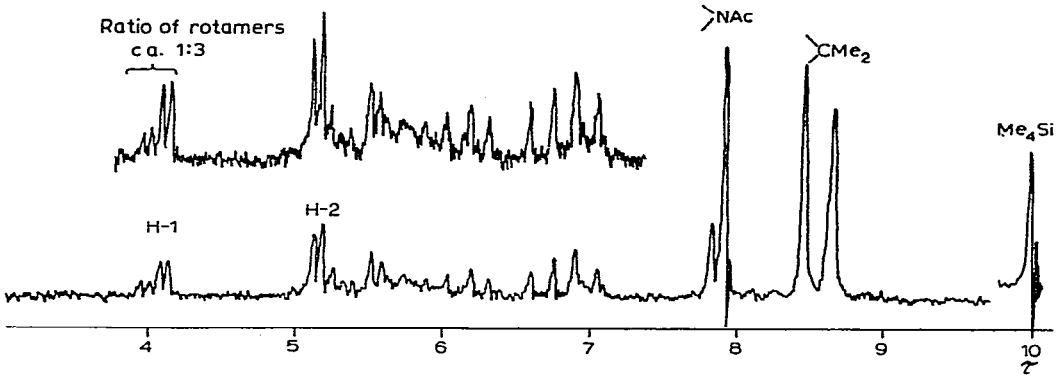
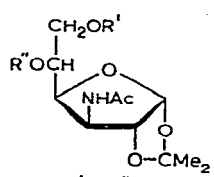


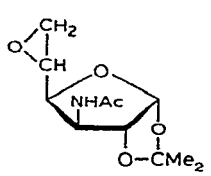
Fig. 1. P.m.r. spectrum (60 MHz) of 3,6-acetylepimino-3,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**8**) in deuteriochloroform; the spectrum should be compared with that of the epimeric L-idose derivative **2** at 100 MHz (Ref. 2).

in *N*,*N*-dimethylformamide at 140° to give 3,6-acetylepimino-5-*O*-benzoyl-3,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**10**). The same benzoate was obtained on direct benzoylation of **2**.

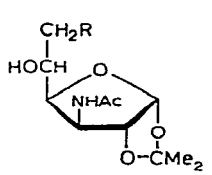
It was suggested[2] previously that either the 6-methanesulphohate **11** or the terminal epoxide **12** might be precursors of the 3,6-acetylepimino derivative **2** formed on solvolysis of the disulphonate **1**. With this in mind, we attempted to cyclize the compounds **14** and **16** in the hope of producing the D-*gluco*-epimino derivative **8**. However, both compounds were principally converted into the diol **13** (characterised as the crystalline dimethanesulphonate **15**) on heating in 95% 2-methoxyethanol–sodium acetate. It seems likely that O(7) participation[10] by the amide group is responsible for the ready solvolysis of the 6-toluene-*p*-sulphonate **14** under these conditions, and ring-opening of the epoxide **16** might be brought about by similar participation. Moreover, there was no indication (from t.l.c.) that any terminal epoxide was formed during the solvolysis of the sulphonate **14**. This evidence does not necessarily preclude the possibility that the monosulphonate **11** is an intermediate in the solvolysis of **1**, since the stereochemistry at C-5 may be critical in the cyclization, depending on whether the hydroxyl group is moving towards an *endo*(unfavourable) or *exo*(favourable) configuration in the transition state, with respect to the ring-system being formed. In the cyclization step **11**→**2**, for example, the C-5 substituent will be placed in the *exo* configuration, whereas it would be required to adopt the less-favourable *endo* configuration in the cyclization of **14**. This point is under examination.



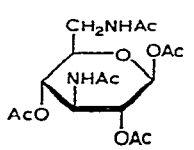
13 R′ = R″ = H
14 R′ = Ts, R″ = H
15 R′ = R″ = Ms



16



17 R = N_3
18 R = NHAc



19

The toluene-*p*-sulphonate **14** was prepared by selective tosylation of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[11] (**13**), and, on brief treatment with methanolic sodium methoxide, it was converted into the epoxide **16**; long reaction times caused opening of the epoxide ring. Neither **14** nor **16** were crystalline, but their structures followed from the fact that each was converted into 3-acetamido-6-azido-3,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**17**) on heating with sodium azide in 2-methoxyethanol. The latter compound was unequivocally identified by its conversion into the known[12] 3,6-diacetamido-1,2,4-tri-*O*-acetyl-3,6-dideoxy-β-D-glucopyranose (**19**) following sequential hydrogenolysis of the azido function, *N*-acetylation, partial hydrolysis with acid, and acetylation.

EXPERIMENTAL

Infrared (i.r.) spectra were generally measured on Nujol mulls with a Perkin–Elmer Infracord spectrophotometer; 60-MHz n.m..r spectra were measured on *ca.* 10% solutions in deuteriochloroform with a Perkin–Elmer R-10 spectrometer, with tetramethylsilane as internal reference. Optical rotations were determined at ~20° with a Perkin–Elmer 141 polarimeter. Silica gel (Hopkin and Williams MFC) was used for column chromatography, and silica gel (Merck GF) was used for analytical t.l.c.; detection was effected with vanillin–sulphuric acid[13].

1,2-O-Isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (**4**). — A solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose[11] (2 g) in *p*-dioxane (10 ml) and 70% acetic acid (40 ml) was heated for 2 h at 60–65°, after which time t.l.c. (chloroform–methanol, 10:1) indicated that hydrolysis of the 5,6-*O*-isopropylidene group was complete. The solvents were evaporated, and the residue was recrystallised from methanol–ether to give the diol **4** (1.7 g), m.p. 150–151°, $[\alpha]_D$ +95° (*c* 1, *N*,*N*-dimethylformamide), +94° (*c* 0.5, acetone) (Found: C, 51.1; H, 5.8; S, 8.6. $C_{16}H_{22}O_8S$ calc.: C, 51.3; H, 5.9; S, 8.6%). The physical constants for **4** differed significantly from those {m.p. 130°, $[\alpha]_D$ +50° (*c* 0.3, acetone)} reported by Heap and Owen[6]. However, the values reported for compound **5** derived from **4** were in close agreement.

1,2-O-Isopropylidene-3,6-di-O-toluene-p-sulphonyl-α-D-allofuranose (**5**). — This compound, m.p. 120–121° [from ethanol–light petroleum (b.p. 40–60°)], $[\alpha]_D$ +67° (*c* 0.5, ethanol), was prepared essentially as described by Heap and Owen[6] who reported m.p. 117–118°, $[\alpha]_D$ +70° (*c* 0.7, ethanol).

6-Azido-6-deoxy-1,2-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (**6**). — A solution of the disulphonate **5** (1.3 g) in *N*,*N*-dimethylformamide (20 ml) containing sodium azide (0.6 g) was stirred for 4 h at 60–70°, during which time complete reaction had occurred. The solvent was removed, the residue was extracted with chloroform (100 ml), and the extract was washed with water (3 × 50 ml) and dried ($MgSO_4$). Evaporation of the extract gave the azide **6** (0.8 g), m.p. 132–133° (from ethyl acetate–hexane), $[\alpha]_D$ +89° (*c* 1, chloroform), ν_{max} 3500 (OH), 2100 (N_3), and 1600 cm^{-1} (OTs); τ 2.35 (4-proton multiplet, aromatic), 4.23 (1-proton doublet,

$J_{1,2}$ 4 Hz, H-1), 7.54 (3-proton singlet, ArMe), 8.48 and 8.71 (3-proton singlets, CMe_2) (Found: C, 47.7; H, 5.2; N, 10.4; S, 8.3. $C_{16}H_{21}N_3O_7S$ calc.: C, 48.1; H, 5.2; N, 10.5; S, 8.0%).

*6-Amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-*D*-allofuranose* (**7**). — A solution of the azide **6** (0.1 g) in dry methanol (10 ml) containing 4% palladised calcium carbonate (0.12 g) was hydrogenated at room temperature for 90 min, whereafter solid material was filtered off with the aid of a Celite pad. Evaporation of the solvent left a white solid which was recrystallised from ethyl acetate–ether to give the amine **7** (85 mg), $[\alpha]_D$ +88° (*c* 1, methanol). The melting point of the amine was ill-defined, showing discoloration at *ca.* 145° before decomposition at *ca.* 173° (Found: N, 3.6; S, 8.3. $C_{16}H_{23}NO_7S$ calc.: N, 3.75, S, 8.6%). The i.r. spectra confirmed that the azido group had been reduced.

*3,6-Acetylepimino-3,6-dideoxy-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**8**). — The preceding amine (0.5 g) in ethanol (20 ml) containing sodium acetate (0.4 g) was heated under reflux for 16 h, and the solvents were then removed. The solid residue was extracted several times with ethyl acetate, and the filtered extracts were evaporated. The residue was taken up in methanol (5 ml) containing acetic anhydride (0.4 ml), and the solution was set aside for 1 h at room temperature before the solvents were removed. Chromatography of the residue on silica gel (with methanol–ethyl acetate, 1:10) afforded the *N*-acetylepimine **8** (0.2 g), m.p. 154–155° [from acetone–light petroleum (b.p. 40–60°)], $[\alpha]_D$ −88.5° (*c* 1, chloroform) (Found: C, 54.5; H, 6.7; N, 5.7. $C_{11}H_{17}NO_5$ calc.: C, 54.3; H, 7.0; N, 5.8%). The i.r. spectrum exhibited prominent absorption bands at 3400 (OH) and 1650 cm^{-1} (NAc), but no absorptions attributable to an NH group were observed. The n.m.r. spectrum of this compound is shown in Fig. 1.

*3,6-Acetylepimino-5-*O*-benzoyl-3,6-dideoxy-1,2-*O*-isopropylidene-β-*L*-idofuranose* (**10**). — Methanesulphonylation of the epimine **8**, in the usual way, gave 3,6-acetylepimino-3,6-dideoxy-1,2-*O*-isopropylidene-5-*O*-methanesulphonyl-α-D-glucofuranose (**9**), $[\alpha]_D$ −47° (*c* 1, chloroform), as an amorphous solid; τ 6.85 (3-proton singlet, OMs).

A solution of the methanesulphonate **9** (0.2 g) in *N,N*-dimethylformamide (20 ml) containing sodium benzoate (0.5 g) was maintained at 140–150° for 5 h, whereupon t.l.c. (chloroform) revealed that a single product had been formed. Solid material was filtered off from the cooled solution, the filtrate was concentrated, and the residue was chromatographed on silica gel (ethyl acetate) to give the benzoate **10** (0.18 g), m.p. 169–170° (from ether), $[\alpha]_D$ −27 ±1° (*c* 1, chloroform), ν_{max} 1730 (benzoate), and 1660 cm^{-1} (NAc) (Found: C, 62.3; H, 6.0; N, 4.25. $C_{18}H_{21}NO_6$ calc.: C, 62.2; H, 6.1; N, 4.0%).

The benzoate resulting from treatment of 3,6-acetylepimino-3,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose[2] (**2**) with benzoyl chloride in pyridine, in the usual way, also had m.p. 169–170°, $[\alpha]_D$ −25.5 ±1° (*c* 1, chloroform). On admixture, the samples had m.p. 169–170°, and their i.r. spectra and X-ray powder photographs were indistinguishable.

*3-Acetamido-3-deoxy-1,2-O-isopropylidene-6-O-toluene-*p*-sulphonyl-α-*D*-glucofuranose* (**14**). — A cold solution of toluene-*p*-sulphonyl chloride (1.8 g) in pyridine (3 ml) was added dropwise to a cooled (0°) solution of the diol[11] **13** (2.4 g) in dry pyridine (5 ml) and, on complete addition, the solution was kept for 6 h at 0° and then overnight at room temperature; t.l.c. (hexane–acetone, 1:3) revealed the presence of a single product, together with a small proportion of unreacted starting material. The reaction mixture was processed in the usual way, and the residue was chromatographed on silica gel (hexane–acetone, 1:3) to give the amorphous sulphonate **14** (3.2 g), $[\alpha]_D$ +39 ±2° (*c* 1, chloroform), ν_{max} 3200 (broad, OH), 1650 and 1550 (NHAc) and 1600 cm^{-1} (OTs); τ 2.44 (4-proton multiplet, aromatic), 4.16 (1-proton doublet, $J_{1,2}$ 4 Hz, H-1), 7.56 (3-proton singlet, ArMe), 7.97 (3-proton singlet, NAc), 8.54 and 8.73 (3-proton singlets, CMe_2) (Found: C, 51.5; H, 6.2; N, 3.3; S, 7.5. $C_{18}H_{25}NO_8S$ calc.: C, 52.0; H, 6.0; N, 3.4; S, 7.7%).

*3-Acetamido-5,6-anhydro-3-deoxy-1,2-O-isopropylidene-α-*D*-glucofuranose* (**16**). — A methanolic solution of sodium methoxide (10 ml, derived from 0.1 g of sodium) was added to a cooled (0°) solution of the sulphonate **14** (1 g) in dry methanol (5 ml) and, after 10 min, the solution was neutralized by the addition of solid carbon dioxide. The residue remaining on evaporation of the solvent was extracted several times with ethyl acetate, and the combined extracts were filtered through a Celite pad and concentrated to give the epoxide **16** (0.6 g), $[\alpha]_D$ −40.5 ±2° (*c* 1, chloroform), as an amorphous material which was homogeneous by t.l.c. The n.m.r. spectrum of **16** showed that the toluene-*p*-sulphonate group had been removed and that opening of the epoxide ring had not occurred; other salient signals were exhibited at τ 4.12 (1-proton doublet, $J_{1,2}$ 4 Hz, H-1), 8.00 (3-proton singlet, NAc), 8.51 and 8.71 (3-proton singlets, CMe_2).

*3-Acetamido-6-azido-3,6-dideoxy-1,2-O-isopropylidene-α-*D*-glucofuranose* (**17**). — (*a*) *From the 5,6-anhydro sugar* **16**. A solution of **16** (0.24 g) in 2-methoxyethanol (10 ml) containing sodium azide (0.5 g) was maintained overnight at 50–55°, during which time complete reaction had occurred. The solvent was removed, the residue was extracted with ethyl acetate, and the filtered extract was concentrated. Chromatography of the residue on silica gel (ethyl acetate) gave the amorphous azide **17** (0.16 g), $[\alpha]_D$ +27 ±1° (*c* 1, chloroform); ν_{max} 3400 (OH), 2100 (N_3), 1650 and 1550 cm^{-1} (NHAc); τ 4.15 (1-proton singlet, $J_{1,2}$ 4 Hz, H-1), 7.95 (3-proton singlet, NAc), 8.49 and 8.70 (3-proton singlets, CMe_2) (Found: C, 46.2; H, 6.0. $C_{11}H_{18}N_4O_5$ calc.: C, 46.15; H, 6.3%).

(*b*) *From the toluene-*p*-sulphonate* **14**. A solution of **14** (1.1 g) in 2-methoxyethanol (30 ml) containing sodium azide (2 g) was treated exactly as described in (*a*) and, after chromatography, gave the azide **17** (0.6 g), $[\alpha]_D$ +27 ±1° (*c* 1, chloroform). The n.m.r. spectrum of the azide was indistinguishable from that obtained in (*a*).

*3,6-Diacetamido-1,2,4-tri-O-acetyl-3,6-dideoxy-β-*D*-glucopyranose* (**19**). — A solution of the azide **17** (0.15 g) in dry methanol (15 ml) was hydrogenated over palladised calcium carbonate (0.2 g) for 2 h at room temperature, whereafter the catalyst was filtered off and the solvent removed. The residue in dry methanol (3 ml)

was treated with acetic anhydride (0.15 ml) for 1 h, and the solution was then evaporated to leave a syrup, presumed to be the diacetamido compound **18**. Partial hydrolysis of **18** was achieved by heating a stirred solution in water (2 ml) for 3 h at 60° in the presence of Amberlite IR-120(H^+) resin (0.2 g). The filtered hydrolysate was concentrated to dryness, and the free sugar was acetylated with acetic anhydride in pyridine. Chromatography on silica gel (ethyl acetate–methanol, 7:1) gave the pentaacetate **19** (0.12 g), m.p. 280° (decomp.), $[\alpha]_D$ −25° (*c* 1, water); ν_{max} 3200 (NH), 1750 (OAc), 1660 and 1550 cm^{-1} (NHAc). Kovář and Jarý[12] reported m.p. 281–282° decomp.), $[\alpha]_D$ −29.8 ±2.4° (in water) for this compound prepared by another route.

*Solvolysis of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-*D*-glucofuranose* (**14**). — A solution of the sulphonate (0.5 g) in 95% 2-methoxyethanol (25 ml) containing sodium acetate (1 g) was heated under reflux for 2 h; t.l.c. (chloroform–methanol, 9:1) revealed the formation of a single component which was chromatographically indistinguishable from the diol[11] **13**. The solvents were removed, the residue was extracted several times with ethyl acetate, and the filtered extracts were concentrated to yield a thick syrup (quantitative), which was methanesulphonylated, in the usual way, to give 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-5,6-di-*O*-methanesulphonyl-α-D-glucofuranose (**15**), m.p. 124–125°, (lit.[2] 123–124°). The sample was identical (i.r. and n.m.r.) with authentic material.

*Solvolysis of 3-acetamido-5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose* (**16**). — A solution of the anhydro sugar (0.18 g) in 95% 2-methoxyethanol (25 ml) containing sodium acetate (0.5 g) was heated under reflux for 3 h; t.l.c. (chloroform–methanol, 9:1) indicated the formation of the diol **13**, together with a small proportion of another component of similar mobility to that of the starting material. The solvolysate was worked up as before, and, after chromatography on silica gel (chloroform–ethanol, 20:1), gave an unidentified, minor component (40 mg) and the diol **13** (0.12 g). The derived dimethanesulphonate **15** had m.p. 123–124°, and was indistinguishable (mixed m.p., i.r., and n.m.r.) from the sample obtained in the previous experiment.

ACKNOWLEDGMENTS

We thank Professor J. Iball for the X-ray powder photographs, and the Saudi Arabian Government for the provision of a studentship (to A.M.M.).

REFERENCES

1 Part XVI: J. S. Brimacombe and A. M. Mofti, *Carbohyd. Res.*, 16 (1971) 167.
2 J. S. Brimacombe and J. G. H. Bryan, *Carbohyd. Res.*, 6 (1968) 423.
3 S. Hanessian, *J. Org. Chem.*, 32 (1967) 163; W. Meyer zu Reckendorf, *Ber.*, 96 (1963) 2019; J. S. Brimacombe, *Fortschr. Chem. Forsch.*, 14 (1970) 367; J. Hildesheim, J. Cléophax, S. D. Géro, and R. D. Guthrie, *Tetrahedron Lett.*, (1967) 5013.
4 D. H. Ball and F. W. Parrish, *Advan. Carbohyd. Chem.*, 24 (1969) 139; J. A. Mills, *ibid.*, 10 (1955) 1.
5 H. Ohrui and S. Emoto, *Carbohyd. Res.*, 10 (1969) 221.
6 J. M. Heap and L. N. Owen, *J. Chem. Soc.* (*C*), (1970) 707.

7 N. A. HUGHES AND P. R. H. SPEAKMAN, *Carbohyd. Res.*, 1 (1966) 341.
8 W. A. SZAREK, S. WOLFE, AND J. K. N. JONES, *Tetrahedron Lett.*, (1964) 2743; H. PAULSEN AND K. TODT, *Advan. Carbohyd. Chem.*, 23 (1968) 115.
9 M. L. WOLFROM, J. BERNSMANN, AND D. HORTON, *J. Org. Chem.*, 27 (1962) 4505.
10 B. CAPON, *Chem. Rev.*, 69 (1969) 480.
11 J. S. BRIMACOMBE, J. G. H. BRYAN, A. HUSAIN, M. STACEY, AND M. S. TOLLEY, *Carbohyd. Res.*, 3 (1967) 318.
12 J. KOVÁŘ AND J. JARÝ, *Coll. Czech. Chem. Commun.*, 34 (1969) 2619.
13 *Chromatography*, E. Merck A. G., Darmstadt, 2nd edn., p. 30.