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FLUOROCARBOHYDRATES*—XXI

5-DEOXY-5-FLUORO-D-XYLOSE, A CRYSTALLINE PENTOFURANOSE

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Abstract—5-Deoxy-5-fluoro-D-xylofuranose has been synthesized by an exchange reaction between 3-O-benzyl-1,2-O-isopropylidene-5-O-toluene-p-sulphonyl-α-D-xylose and tetrabutyl ammonium fluoride. The structure of the fluoro sugar is established by NMR measurements at 100 MHz and 220 MHz.

INTRODUCTION

EXCHANGE of primary and secondary sulphonyloxy groups on substituted carbohydrates by F has been successfully accomplished in a number of cases, as reviewed recently.[1] The reaction, however, is powerfully influenced by stereochemical factors and by effects of electronegative groups in close proximity to the sulphonyloxy group. The present investigation is concerned with a further example of this method of synthesis in the carbohydrate series, and leads to 5-deoxy-5-fluoro-D-xylose. Derivatives of the 3-deoxy-3-fluoro-[2] and 3,5-dideoxy-3,5-difluoro-D-xylose have been reported.[3]

RESULTS AND DISCUSSION

Contrary to expectations, 5-O-sulphonyloxy esters of substituted xylofuranoses proved to be markedly resistant to exchange using KF in methanol, ethandiol, dimethyl sulphoxide, formamide and acetamide. In the mesyl and tosyl esters studied, the 1 and 2 positions were blocked by an isopropylidene group, and an O-benzyl or O-*p*-nitrobenzyl group was present at C-3. The desired exchange was achieved, however, by means of tetra-n-butyl-ammonium fluoride[4,5] in acetonitrile acting on the benzyl ether (**1**). With the *p*-nitrobenzyl ether, highly coloured products resulted. The reaction is highly dependent on the anhydrous nature of the fluorinating agent and on its method of preparation. For this reason rather full details are given in the experimental section.

In addition to the 5-deoxy-5-fluoro derivative (**2**), a minor product (6%) of the reaction is 3-O-benzyl-5-deoxy-1,2-O-isopropylidene-β-L-threo-pent-4-enofuranose (**3**) which results from a competing elimination reaction. Removal of the benzyl group from **2** by hydrogenolysis furnished a crystalline 5-deoxy-5-fluoro-1,2-O-isopropylidene-α-D-xylopentose (**4**), which on acid hydrolysis gave the free 5-deoxy-5-fluoro-D-xylopentose (**5**). The latter fluorosugar is of interest because it is one of the few reducing pentofuranoses to be isolated in crystalline form. The absence of evidence of mutarotation of the sugar, coupled with the presence of α and β forms of the anomeric hydrogen in proton NMR spectra, suggests that the inversion is very rapid.

A previous paper[6] has dealt in detail with the full NMR analysis of xylofuranoses

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related to the above compounds, in cases where complete assignments can be made. In general, the fluoro-analogues follow the same type of H shifts and couplings at 100 and 220 MHz, but these are augmented by the effects of the fluorine at C-5. Extensive NMR studies of fluoro sugars have been made by L. D. Hall *et al.*[11]

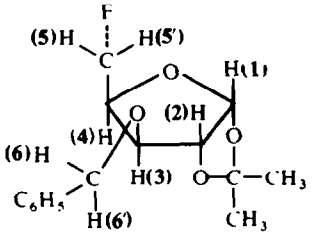
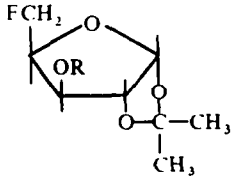
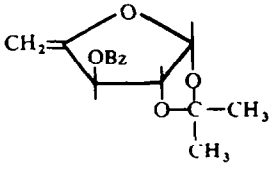


FIG 1. Designation of protons (no distinction is made between H(5) and (5') nor between H(6) and (6')

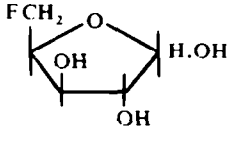
The 3-O-benzyl-5-fluoro-sugar (**2**, Fig 1) at 100 MHz (in $CDCl_3$) showed the following peaks: singlet τ 2·69 (5 aromatic protons), doublet τ 4·06, J_{12} 3·4 Hz (one proton), and two singlets τ 8·51 and 8·68 (CH_3-protons). The spectrum was complex in the region τ 5·2 to 5·7 and around τ 6·01. The fine structure (Fig 2) as revealed at 220 MHz gave the assignments set out in Table 1. The complex region τ 5·2 to τ 5·7 contains signals from H-2, H-4, H-5, H-5', H-6 and H-6'. The greater electronegativity



2, R = benzyl
4, R = H



3 (Bz = benzyl)



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of F results in the shift of the signals from H-5 and H-5′ (τ 6·7 in the iodo analogue) downfield into this complex region. The doublet, τ 6·03 is ascribed to H-3 by analogy[6] with the iodocompound. The non-equivalent methylene protons (H-6 and H-6′) give

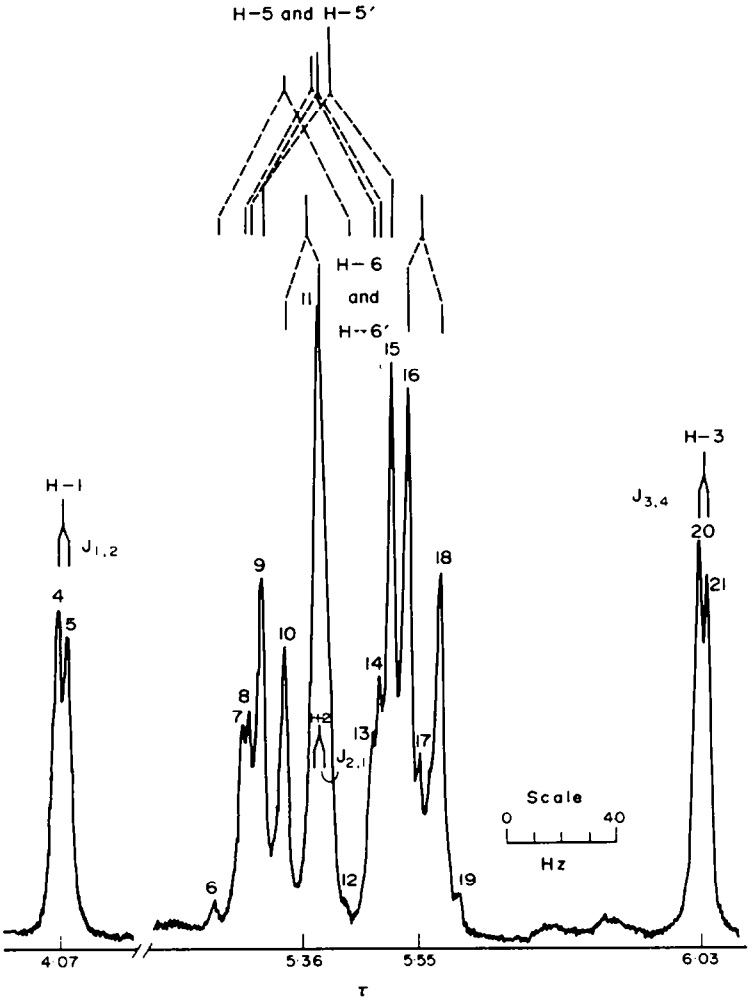

FIG 2. Expansion of parts of 220 MHz NMR spectrum of 3-O-benzyl-5-deoxy-5-fluoro-1.2-O-isopropylidene-α-D-xylose (**2**) in $CDCl_3$ (181 mg in 0·7 ml: 13°) (aromatic and isopropylidene protons not shown)

rise again to a quartet (τ 5·55, 5·36; $J_{6,6'}$ 12 Hz), as has been observed previously in the iodo analogue.[6] The protons H-5, H-5′ and H-4 form an ABX system; H-5 and H-5′ have scarcely different chemical shifts and are split by F into the expected sets of peaks (**6** to **9** and **12** to **15**. Fig 2 and Table 1) with a coupling constant of 47 Hz. The H-4 multiplet shows splitting attributed to H-3 and F.

The 5-deoxy-5-fluoro-isopropylidene sugar (**4**) has NMR properties at 100 (34°) and 200 MHz (10°) in accord with the expected proton couplings, the AB part of the

ABX system for H-5, H-5′ and H-4 being further split by F with J value 47 Hz (Fig 3). The ^{19}F spectrum (Fig 4) for this compound in acetone at 20° confirmed this H–F coupling and further showed that the J value for F–H(4) was 16 Hz. The parent sugar 5-deoxy-5-fluoro-D-xylose in D_2O (at 100 MHz, 34°, with DDS as internal standard) showed two low field doublets τ 4·56 (splitting 4·2 Hz) and τ 4·75 (splitting 2·5 Hz) tentatively identified as arising from the α- and β-anomeric protons respectively.

TABLE 1. ASSIGNMENT OF PROTON RESONANCES (220 MHz) OF 3-O-BENZYL-5-DEOXY-5-FLUORO-1,2-O-ISOPROPYLIDENE-α-D-XYLOSE (IN $CDCl_3$)

Peak No. (Fig 2)	Chemical shift from (H_2)‡ reference shift	Integration‡	Multiplicity	Splittings (Hz) (measured on the expansion) (Fig 2)	Assignment
1	1606	5H	c		Aromatic protons
2	1603				
3	1593		s		$CHCl_3$*
4	1307	1H	d	3·4	H-1
5	1303				
6	1050	3H	see text	9·8, 11·9, 16·0	Half of H-5 and H-6 pattern
7	1041				
8	1039				
9	1036				
10	1026		q and d	44·4, 12·0	H-6 and H-6′ (q) and H-2 (d)
11†	1016				
16	984				
18	970				
12	1005	3H	see text	9·8, 11·9, 16·0	Half of H-5 and H-5′ pattern
13	994				
14	992				
15	989				
17	976		see text		Part of H-4 multiplet
19	961				
20	876	1H	d	3·0	H-3
21	873				
22	328	3H	s		Isopropylidene group
23	292	3H	s		
24	0		s		TMS reference
	±2 (Hz)			$\delta_{6,12} = \delta_{7,13} = \delta_{8,14} = \delta_{9,15} = 46·9 \pm 0·3$	
				Fine splitting of **20** and **21** ⩽ 0·7 Hz	

* Solvent impurity.
† Peak **11** contains 3 unseparated peaks.
‡ Data from unexpanded spectrum (not shown).

The 4,5-unsaturated sugar (**3**) exhibited, at 220 MHz (10° in $CDCl_3$ or C_6H_6) magnetic non-equivalence of the benzyl CH_2 protons, as has been observed in analogues,[6,7] the coupling constant (J, 11·7 Hz) being practically identical in both solvents. The chemical shift difference was substantially different in the two solvents.

45·4 Hz in $CDCl_3$ and 69·7 Hz in C_6H_6. In this case, as already reported in other cases, geminal proton coupling in CH_2 was small, but in $CDCl_3$ both undergo long range 1,3-allylic coupling over four bonds with H-3 (J 1·4 Hz). The effect of C_6H_6 is to promote downfield shifts of the long range couplings, and resolution of composite peaks arising from CH_2.

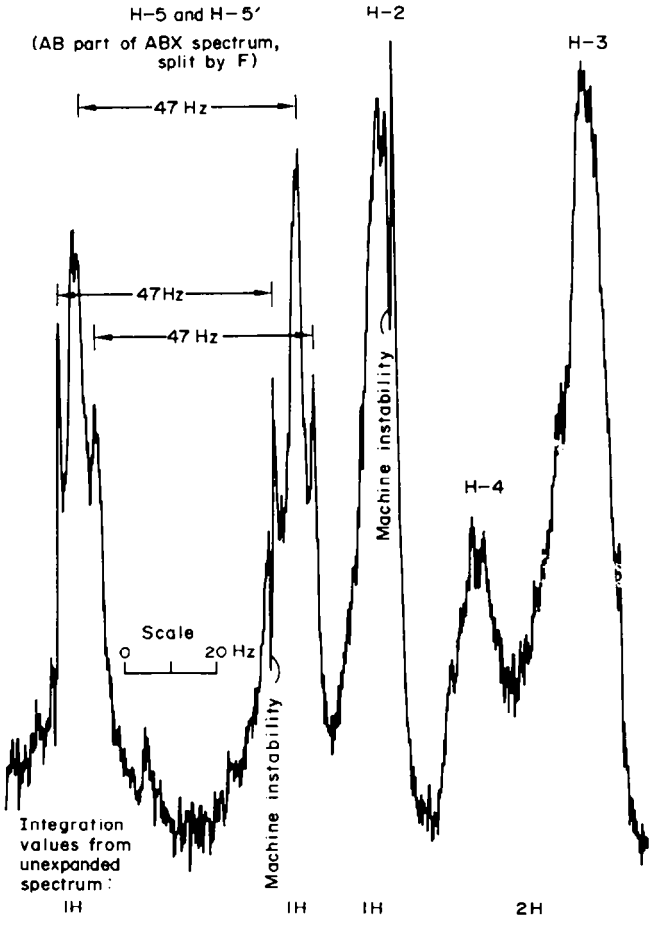

FIG 3. Expansion of part of 220 MHz NMR spectrum of 5-deoxy-5-fluoro-1,2 o-isopropylidene-α-D-xylose in $CDCl_3$ (31 mg/0·7 ml; 10°); aromatic anomeric, hydroxyl, and isopropylidene peaks not shown

The 3,5-anhydro-1,2-O-isopropylidene-α-D-xylofuranose[8] (7) gave spectra at 100 and 200 MHz which could be analyzed on a first order basis. As with 3, a weak or vanishing coupling between H-2 and H-3 was inferred. The protons of the CH_2 of the four-membered anhydro ring each have significantly different chemical shifts (τ 5·29 and τ 5·77), and each is coupled to H-4 giving three quartets. The H-4 quartet is further coupled to H-3 but because $J_{3,4}$ is equal to $J_{4,5}$ a sextet, rather than octet

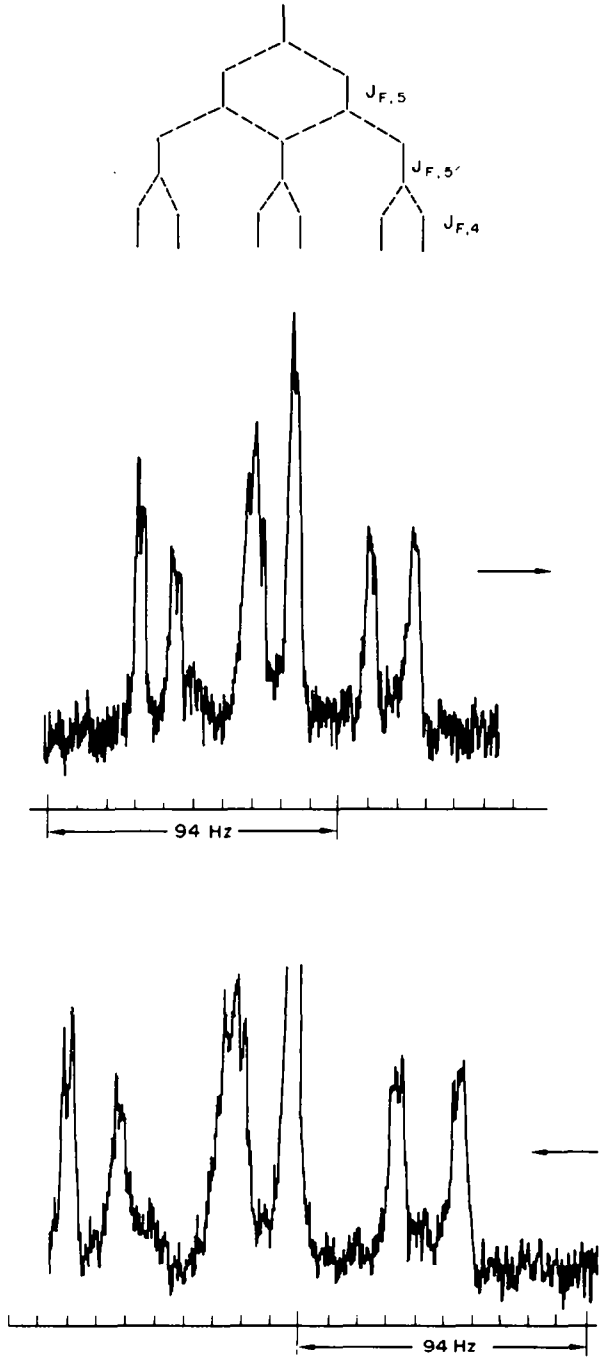

FIG 4. ^{19}F NMR spectrum at 94 MHz of 5-deoxy-5-fluoro-1.2-O-isopropylidene-α-D-xylose (**4**) in acetone (560 mg in 1 ml. 20°). Arrow indicates direction of sweep

is obtained. In this case measurements in pyridine were a successful means of separating overlapped doublets.

The 5-fluorosugar readily gave the crystalline 2.5-dichlorophenylhydrazone and, on reduction with KBH_4 gave 1-deoxy-1-fluoro-L-xylitol (**6**).

The NMR results are consistent with the structures proposed and suggest an extensive degree of non-planarity of the furanose ring system in **4**. The results agree with the high resolution NMR studies carried out independently on 3-O-benzyl-5-deoxy-1,2-O-isopropylidine-β-D-arabinose.[7]

EXPERIMENTAL

Chromatographic techniques and other general methods were as described previously.[9]

NMR measurements. Proton NMR spectra were measured at 100 MHz. by Mrs. E. Richards using a Perkin–Elmer R14 spectrometer. Tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DDS) were used as standards in organic and aqueous solns respectively. Test compounds were approx 0·25 mmole/ml. Measurements at 220 MHz were carried out by Dr. R. A. Dwek using a Varian HR220 instrument with a superconducting magnet. These facilities were generously provided by Imperial Chemical Industries Ltd. Fluorine (^{19}F) NMR spectral measurements, also performed by Dr. Dwek, were made at 94 MHz on an instrument constructed by Professor Richards and co-workers.

Tetra-n-butyl-ammonium fluoride. Aqueous HF (10% w/v) was added slowly to aqueous tetra-n-butyl-ammonium hydroxide (100 ml) until the pH value began to fall. The reaction was completed by titration with dilute HF (3%) to pH 7. The resulting light brown soln was diluted with H_2O to a final volume of 300 ml (*ca* 0·5 M). When cooled in ice, fine crystals of the clathrate $(C_4H_9)_4$ NF. 32·8 H_2O were deposited.[10] This product was filtered, washed with cold H_2O and finally dried in air (yield 72 g; m.p. 23–25°). A second crop of clathrate (32 g) was obtained by concentration of mother liquors, dilution to *ca* 0·5 M and cooling to 0°. The clathrate could be stored in a polythene container at 0° for several weeks. For exchange reactions, the calculated quantity of clathrate was heated to 50° at 15 mm in a round-bottomed flask attached to a rotary evaporator. The melted solid gave a viscous syrup as H_2O was lost. Finally a colourless glass was formed which was stored and further manipulated in a dry box. While cooling, the glass was dislodged from the walls of the flask with a glass rod to give soft white granules of a gel-like material. This material was stored over P_2O_5 *in vacuo* for 24 hr in a desiccator within the dry box. The resulting granules were pulverised with a glass rod and the resulting solid further desiccated over P_2O_5 until no further H_2O was removed (4 days). The final product was extremely hygroscopic and was always manipulated in the dry box.

3-*O-Benzyl*-1,2-*O-isopropylidene*-5-*O-toluene*-p-*sulphonyl*-α-D-*xylofuranose* (**1**). This compound, prepared by the method of Young, Kent and Dwek[6] had $[\alpha]_D^{21}$ −29·0° (*c* 1·3 in $CHCl_3$) R_f 0·4 (TLC. $CHCl_3$, Kieselgel PF_{254}).

3-*O-Benzyl*-5-*deoxy*-5-*fluoro*-1,2-*O-isopropylidene*-α-D-*xylofuranose* (**2**). The tosylate **1** (4·9 g) and anhyd. tetra-n-butyl-ammonium fluoride (desiccated from 60 g of clathrate) in MeCN (25 ml) was refluxed for 6 hr. The resulting brown soln was cooled, poured into Et_2O (100 ml), washed with H_2O (3 × 25 ml) and dried ($MgSO_4$). TLC ($CHCl_3$, Kieselgel PF_{254}) revealed several components from which two main products (R_f 0·55, 0·75) were separated by PLC (developed twice in $CHCl_3$–petroleum ether (1:2)). The first product (R_f 0·55) was homogeneous and was obtained as a syrup (1·53 g, 48%) n_D^{19} 1·4969. $[\alpha]_D^{22}$ −40·5° (*c*, 2·5 EtOH). (Found: C, 64·0; H, 6·9; F, 6·4. $C_{15}H_{19}FO_4$ requires C, 63·9; H, 6·8; F, 6·7%). This product was identified by NMR spectroscopy as the 3-*O-benzyl*-5-*deoxy*-5-*fluoro*-1,2-*O-isopropylidene*-α-D-*xylofuranose* (**2**). The second component (R_f 0·75; 0·18 g, 6%) was a syrup n_D^{19} 1·5115. $[\alpha]_D^{22}$ −29·1° (*c*, 1·43 EtOH), identified as 3-*O-benzyl*-5-*deoxy*-1,2-*O-isopropylidene*-β-L-*threo*-*pent*-4-*eno*-*furanose* (**3**) on the basis of NMR. (Found: C, 68·1; H, 6·6. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

5-*Deoxy*-5-*fluoro*-1,2-*O-isopropylidene*-α-D-*xylofuranose* (**4**). The 3-benzyl derivative **2** (2·6 g) in EtOH (20 ml) was hydrogenolyzed at room temp and atmospheric press. in the presence of Pd/C 10% (500 mg). When uptake (250 ml) of H_2 had ceased (3 hr), the filtered soln was concentrated to a colourless syrup (1·7 g, 98%) which crystallized spontaneously. After recrystallization from light petroleum (60–80°)–EtOH (200:1 v/v) the *isopropylidene derivative* **4** had m.p. 86°. $[\alpha]_D^{23}$ −20·6 (*c*, 1·0 $CHCl_3$). (Found: C, 50·1; H, 7·0; F, 9·7. $C_8H_{13}FO_4$ requires C, 50·0; H, 6·8; F, 9·9%).

5-*Deoxy*-5-*fluoro*-D-*xylofuranose* (**5**). The isopropylidene derivative **4** (0·54 g) in 0·01 M H_2SO_4 (20 ml) was kept at 100° for 3 hr. The cooled soln, neutralized with Dowex 1-X8 (CO_3^{2-}) 200–400 mesh (10 ml), was

freeze-dried to a syrup which slowly crystallized. After recrystallization from EtOAc, the *fluoroxylose* **5** had m.p. 77°–78°. $[\alpha]_D^{24}$ +52·7° (*c*. 1·7 H_2O; after 5 min and after 24 hr). (Found: C. 40·2; H. 5·9; F. 11·5. $C_5H_9FO_4$ requires C. 39·5; H. 6·0; F. 12·5%). The sugar reduced copper reagents and gave a slight colouration with Schiffs reagent after 30 min.

Treatment of the fluorosugar **5** (156 mg) with an equal weight of 2.5-dichlorophenylhydrazine in hot MeOH gave *5-deoxy-5-fluoro-*D*-xylose-2.5-dichlorophenylhydrazone*, crystallized and recrystallized from H_2O m.p. 100°. (Found: C. 42·5; H. 4·6; F. 6·3; N. 8·8. $C_{11}H_{13}Cl_2FN_2O_3$ requires C. 42·5; H. 4·2; F. 6·1; N. 9·0%).

1-*Deoxy-1-fluoro-*L*-xylitol* (**6**). The 5-fluorosugar **5** (0·5 g) was reduced with KBH_4 (178 mg) in EtOH (10 ml) at 0° for 30 min and then at 20° for 3 hr. MeOH (100 ml) and methanolic HCl (10 ml. 10% v/v) were added and the soln refluxed. while slowly distilling methyl borate. The boron-free soln was neutralized ($PbCO_3$). filtered and diluted with water (10 ml). After passage through mixed-bed resin (Amberlite MB-3. 9 × 0·7 cm). the soln was freeze-dried. The resulting syrup. chromatographically homogeneous. was identified as 1-*deoxy-1-fluoro-*L*-xylitol* (0·47 g) n_D^{25} 1·4729. (Found: F. 12·0. $C_5H_{11}FO_4$ requires: F. 12·3%).

3.5-*Anhydro-1.2-O-isopropylidene-α-*D*-xylofuranose* (**7**). This was obtained from the 5-O-mesylate[6] by the method of Levene and Raymond.[8] as colourless needles m.p. 16–17°; b.p. 63–64°. 0·01 mm. n_D^{20} 1·4551 $[\alpha]_D^{21}$ +12·6 (*c*, 2·4 $CHCl_3$) (Lit.[8] m.p. 16·9–17·3° b.p. 63–64°/0·1 mm $[\alpha]_D^{20}$ +11·7° (*c*, 2·4 $CHCl_3$)).

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