FLUORINATED CARBOHYDRATES*

PART XI[1]. 6-DEOXY-6-FLUORO-D-GLUCOSE: AN IMPROVED SYNTHESIS AND THE GLYCOSYL FLUORIDE DERIVATIVES

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ABSTRACT

The original synthesis of 6-deoxy-6-fluoro-D-glucose, which involves as the key stage a fluoride-displacement reaction on 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-mesyl-α-D-glucofuranose, has been improved. Treatment of methyl 6-*O*-tosyl-α-D-glucopyranoside with potassium fluoride in boiling ethane-1,2-diol affords a mixture of 6-deoxy-6-fluoro and 3,6-anhydro derivatives of D-glucose. The α,β-pyranose equilibrium in aqueous solution is not significantly changed on conversion of D-glucose into the 6-deoxy-6-fluoro derivative. Treatment of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-fluoro-α,β-D-glucopyranose with hydrogen fluoride at −10° yields, in addition to the expected acetylated α-D-glycosyl fluoride, 3,4-di-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl fluoride. On the basis of n.m.r. data, the preferred rotamer about the C-5–C-6 bond in 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-fluoro-α- and -β-D-glucopyranose and the corresponding glycosyl fluorides was identified as having F-6 and H-5 antiplanar. A ^5J F–F coupling was observed in each glycosyl fluoride.

INTRODUCTION

As part of a programme concerned with the evaluation of gross, anti-tumour activity *in vivo* of deoxyhalogenoglucoses and their utilisation[2] in establishing structure–activity relationships for substrates of the hexokinase isozymes of normal and tumour cells[3], 6-deoxy-6-fluoro-D-glucose and the bromo and chloro analogues were required. Since, for compounds of relatively low toxicity, the evaluation of anti-tumour activity against a range of experimental animal tumours can involve decagram quantities of materials, short, high-yielding syntheses are desirable.

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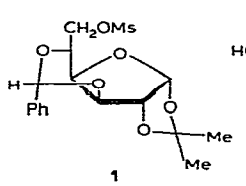
The synthesis of the 6-deoxy-6-halogeno-D-glucoses was therefore re-investigated.

RESULTS AND DISCUSSION

The original synthesis[4] of 6-deoxy-6-fluoro-D-glucose, which comprised six stages starting from D-glucose, included the treatment of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-mesyl-α-D-glucofuranose (**1**, derivable from D-glucose in four stages) with potassium fluoride dihydrate in methanol. Potassium fluoride in ethane-1,2-diol[5] or *N*,*N*-dimethylformamide[6] was subsequently employed. 1,2-*O*-Isopropylidene-6-*O*-mesyl-α-D-glucofuranose (**2**), the immediate precursor of **1**, can be prepared much more conveniently than by the 3-stage procedure[7], D-glucose → 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose → 1,2-*O*-isopropylidene-α-D-glucofuranose → **2**, by treatment of D-glucose with boric acid–acetone–conc. sulphuric acid followed by mesylation of the crude 3,5-borate complex[8]. This procedure is suitable for large-scale work.



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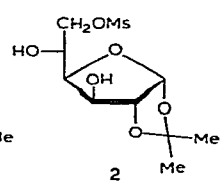

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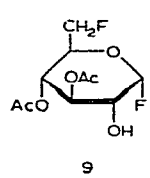

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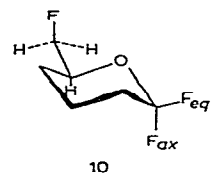

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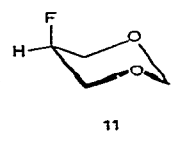

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Hydrolysis of the cyclic acetal residues from **1** to give 6-deoxy-6-fluoro-D-glucose was more conveniently effected with the H^+ form of a cation-exchange resin[9] than with mineral acid. 6-Bromo- (**3**) and 6-chloro-6-deoxy-D-glucose, required for comparison with the fluoro analogue, were prepared by treatment of the methanesulphonate **1** with lithium bromide or chloride in *N*,*N*-dimethylformamide, followed by resin-catalysed hydrolysis. Likewise, 6-bromo- (**4**) and 6-chloro-6-deoxy-D-galactose were obtained from 1,2:3,4-di-*O*-isopropylidene-6-*O*-mesyl-α-D-galactopyranose. The bromo sugars **3** and **4** have not previously been reported crystalline.

In seeking an alternative synthesis of 6-deoxy-6-fluoro-D-glucose, the reaction of methyl 6-*O*-tosyl-α-D-glucopyranoside with potassium fluoride in boiling ethane-1,2-diol was investigated. Reaction was rapid ($\leqslant 3$ min), but a mixture of methyl 3,6-anhydro-α-D-glucopyranoside and methyl 6-deoxy-6-fluoro-α-D-glucopyranoside was formed. The need for chromatographic separation of the components of the mixture and the poor yield of the fluoro derivative ultimately isolated via acetylation and deacetylation largely deprived the route of convenience.

The ^{19}F n.m.r. spectrum of a solution of 6-deoxy-6-fluoro-D-glucose in D_2O showed resonances (upfield relative to external C_6F_6) at 6363 Hz (sextet, β anomer, $J_{F,6} = J_{F,6'} = 47$, $J_{F,5}$ 27.5 Hz) and 6432 Hz (sextet, α anomer); αβ-ratio ~1:1.35 (*cf.* the corresponding ratio[10] of ~1:1.8 for an aqueous solution of D-glucose). For a solution in methyl sulphoxide-d_6 (internal Me_4Si), ^1H resonances were observed[11] at δ 6.4 (doublet, $J_{1,OH}$ 4 Hz, HO-1 of α anomer) and 6.75 Hz (doublet, $J_{1,OH}$ 6.5,

HO-1 of β anomer); $\alpha\beta$-ratio ~19:1. Therefore, the form of 6-deoxy-6-fluoro-D-glucose crystallising from ethyl acetate–ethanol and showing downward mutarotation on dissolution in water is almost pure α anomer.

6-Deoxy-6-fluoro-D-glucose was readily converted into the α-(**5**) and β-tetra-acetates (**6**) by conventional procedures (see Experimental). Treatment of an $\alpha\beta$-mixture of the tetra-acetates with anhydrous hydrogen fluoride at $-10°$ (thermodynamic control[12]) gave a mixture of four products of which the major components were 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl fluoride (**7**, ~25%) and 3,4-di-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl fluoride (**9**, ~30%). The conversion **9** → **7**, effected by treatment with acetic anhydride–pyridine, established the structural relationship of the compounds. The structure of **9** was established on the basis of n.m.r. data. Whereas the chemical shift differences ($\Delta\tau$) for the respective pairs of protons H-1,3,4,5 in **7** and **9** were in the range 0.05–0.23 p.p.m., the value for H-2 was 1.20 p.p.m. Since the proton in the group *H*COAc is deshielded more[13] than that in *H*COH, the higher field position (τ 6.35) of the signal for H-2 in **9** indicates a free hydroxyl group at C-2. Loss of Ac-2 in the treatment of pentose tetra-acetates with anhydrous hydrofluoric acid has been observed by Pedersen[14]. The formation of products other than **7** and **9** in the reaction of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-fluoro-$\alpha\beta$-D-glucopyranose with anhydrous hydrogen fluoride is not surprising, since the reaction of β-D-glucopyranose penta-acetate with this reagent at room temperature gives, *inter alia*, products having the *manno* and *altro* configurations[15].

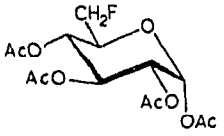
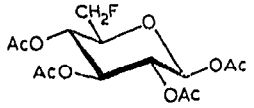
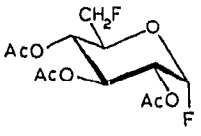
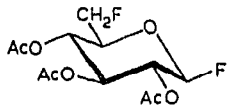
Conventional treatment of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-fluoro-$\alpha\beta$-D-glucopyranose with hydrogen bromide–acetic acid gave the α-D-glycosyl bromide, from which 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-β-D-glucopyranosyl fluoride (**8**) was obtained by reaction with silver fluoride in acetonitrile. Deacetylation (methanolic ammonia) of **7** and **8**, gave, respectively, 6-deoxy-6-fluoro-α- and β-D-glucopyranosyl fluoride as crystalline solids of moderate stability.

The conformation of deoxyfluorohexoses can be determined[13] with reasonable precision on the basis of ^{1}H n.m.r. data. It therefore follows that, for compounds which are relatively rigid and which contain a fluorine atom attached to a ring carbon atom, the steric relationship of the fluorine atom to each proton (or other fluorine atom) in the same molecule is also defined. Thus, in appropriate series of compounds, the steric dependence of the magnitude and sign of vicinal and long-range (^4J and ^5J) F–H and F–F couplings can be investigated. The determination of such a relationship is of potential importance, since it would make feasible the use of ^{19}F resonances to probe the conformation of appropriate, fluorine-containing molecules, or parts thereof, where ^{1}H resonances cannot easily be used for this purpose. Thus, in principle, the conformation of flexible molecules, of molecules in aqueous solution, and of substrates in enzyme–substrate complexes could be investigated.

Extensive data[16] on vicinal F–H and F–F couplings are now available, but data on ^4J and ^5J couplings are relatively meagre. ^5J F–H couplings involving H-1 are possible in hexopyranose derivatives containing a fluorine atom at positions 4 or 6, and the corresponding F–F couplings can occur in the glycosyl fluorides of

TABLE I

J VALUES (Hz) FOR COMPOUNDS 5–8

		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{F-6,5}$	$J_{6,6'}$	$J_{F-6,6}$	$J_{F-6,6'}$	$J_{F-1,1}$	$J_{F-1,2}$	$J_{F-1,F-6}$
	5	3.8	10.2	9.4	10.2	6.4 (sum)		23.1		46.9 (mean)				
	6	7.5	[b]	[b]	9.6	2.3[a]	4.2[a]	21.9	10.7	47.0	46.8			
	7	2.7	9.9	9.4	10.0	2.2	3.5	23.9	10.8	47.0 (mean)		52.4	23.8	⩽0.2
	8	5.5	[b]	[b]	9.0	7.5 (sum)		20.6		46.6 (mean)		52.7	10.4	0.9

[a] By ABX analysis; splittings 2.8, 3.7. [b] Indeterminate.

these molecular types. N.m.r. data for the 6-fluoro compounds **5–8** are given in Tables I and II; the data for 4-deoxy-4-fluoro-D-glucose derivatives are reported in the following paper.

TABLE II

CHEMICAL SHIFT DATA[a] (τ VALUES; Φ_c VALUES) FOR COMPOUNDS **5–8**

	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*OAc*	Φ_c	
									F-1	*F-6*
5	3.67	4.94	4.51	4.87	5.90	←5.56→		7.839, 7.954 7.986, 8.003	—	233.7
6	4.26	←4.62–5.00→			6.16	5.51	5.57	7.903, 7.963 7.984, 7.996	—	233.5
7	4.25	5.06	4.50	4.83	5.97	5.49	5.55	7.919, 7.956 7.988	150.4	234.8
8	4.60	←4.75–5.07→			6.05	←5.49→		7.920, 7.955 7.980	137.0	232.2

[a]Determined for solutions in $CDCl_3$–CCl_3F–Me_4Si (16:3:1, v/v) using a modified Varian HA-100 spectrometer operating in the locked, frequency-sweep mode at 100 MHz for ^1H resonances, and at 94 MHz for ^{19}F resonances.

The magnitude of the vicinal ^1H–^1H couplings shown in Table I for compounds **5–7** are consistent with each molecule being essentially in the $^4C_1$ conformation. However, for **8**, because of the known[10,17], large anomeric effect associated with a glycosyl fluorine substituent, there may be a significant contribution from other conformations to the time-averaged conformation, and/or distortion of the $^4C_1$ conformation. This is suggested by the relatively low value (9 Hz) of $J_{4,5}$, but further analysis was not possible because values for $J_{2,3}$ and $J_{3,4}$ could not be obtained. The values (3.8, 7.5 Hz) of $J_{1,2}$ for **5** and **6** correspond closely with those[18] (3.5, 8.0) for α- and β-D-glucopyranose penta-acetates. Likewise, the values for $J_{1,2}$ (2.7, 5.5 Hz) and $J_{F-1,2}$ (23.8, 10.4) for **7** and **8** may be compared with those[19] (2.7, 6.6 and 23.8, 12.0) for 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosyl fluorides.

Although a detailed evaluation of the rotamer populations about the C-5–C-6 bond is complicated by the effects of rapid rotation about this bond, an adequate indication of the favoured rotamer can be based on the magnitude of the F-6–H-5 coupling. The values (20.6–23.9 Hz) of $J_{F-6,5}$ for **5–8** are somewhat lower than those (27–29 Hz) previously reported for 6-deoxy-6-fluoro-D-glucopyranose derivatives[20] and for vicinal, diaxial F–H couplings (25–30 Hz) of deoxyfluoropyranosides[19] (*cf.* 12–14.5 Hz for *gauche* coupling); nevertheless, they indicate that the preponderant rotamer is that (**10**) where F-6 and H-5 are antiplanar.

This simple, direct evaluation is supported by the H-5–H-6 couplings, since there is a monotonic relationship between the values of $J_{F-6,5}$ and the sum $J_{5,6}+J_{5,6'}$; this unique agreement appears to be more than fortuitous. A similar conformation (**11**) is preferred by 5-fluoro-1,3-dioxane[21]. It may be noted that the lowest value

(20.6 Hz) of $J_{F-6,5}$ was observed for **8**, and this could reflect the time-averaging effect noted above and be consequent on the significant contribution of other conformations arising from the anomeric effect associated with the equatorial F-1 substituent.

No long-range (^5J) F–H coupling was detected for F-1 or F-6 in **5–8**, but long-range F–F coupling was observed for both **7** ($\leqslant 0.2$ Hz) and **8** (0.9 Hz). Although the precise relative orientation of F-1 and F-6 in these compounds cannot be stated, it appears that the geometrical arrangement of F-6–F-1*eq* (**10**) is more favourable for coupling than is that of F-6–F-1*ax*. The relationship between the extent of planar zig-zag arrangement of the intervening bonds and the magnitude of ^5J couplings has not been established, but it may be noted (see **10**) that, whereas four of the bonds between F-1*eq* and F-6 are in a planar zig-zag arrangement with the C-6–F bond rotated 120° out of the plane, only the three central bonds between F-1*ax* and F-6 are planar zig-zag. A planar zig-zag arrangement of four bonds with the C-6–H-6 bond out of the plane has been inferred[22] for F–H-6 in 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-β-D-glucopyranose, for which $J_{F,6}$ is 1.5 Hz. Closely related, but relatively rigid, geometries should be present in 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α- and -β-D-galactopyranosyl fluorides, and the synthesis of these compounds is in hand.

From the chemical shift data in Table II, it is clear that the Φ_c value for F-6 is not significantly influenced by the orientation or nature of the C-1 substituent. The Φ_c values for F-1 (150.4 and 137.0) for the α- (**7**) and β-glycosyl fluoride (**8**) are similar to those[19] (149.9, 137.8) for 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosyl fluoride.

The biological activity of 6-deoxy-6-fluoro-D-glucose will be described in detail elsewhere, but it may be noted that selective activity was found against the primary growth of the RI lymphoma, a transplantable, metastasising mouse-tumour.

EXPERIMENTAL

Melting points are corrected. Thin-layer chromatography (t.l.c.) was performed on Kieselgel 7731 (Merck), and detection was effected with conc. sulphuric acid. Kieselgel 7734 was used for column chromatography. Unless stated otherwise, optical rotations were determined on 1–2% solutions in chloroform (path-length 10 cm), using a Perkin–Elmer 141 polarimeter.

Following treatment[5] of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-mesyl-α-D-glucofuranose[4] (**1**) with potassium fluoride in boiling ethane-1,2-diol, 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (14%), m.p. 125–125.5° (lit.[23] m.p. 126°), was isolated, in addition to 3,5-*O*-benzylidene-6-deoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (58%).

Action of potassium fluoride on methyl 6-O-tosyl-α-D-glucopyranoside. — A solution of methyl 6-*O*-tosyl-α-D-glucopyranoside[24] (20 g) and anhydrous potassium fluoride (20 g) in ethane-1,2-diol (100 ml) was boiled under reflux for 3 min. T.l.c. (ethyl acetate) then revealed the disappearance of starting material and the formation

of two products. The mixture was evaporated at 95°/1 mmHg, and the residue was eluted from Kieselgel with ethyl acetate to give, as the faster-running component, methyl 3,6-anhydro-α-D-glucopyranoside (1.6 g, 16%), m.p. 107–108° (from ethyl acetate), $[\alpha]_D^{30}$ +66° (*c* 1.5, methanol); lit.[25] m.p. 108°, $[\alpha]_D$ +56° (water). The diacetate had m.p. 131–132°, alone and in admixture with an authentic sample (kindly provided by Dr. J. M. Webber), and $[\alpha]_D^{30}$ +105°; lit.[26] m.p. 131–132°, $[\alpha]_D^{22}$ +106°. The n.m.r. spectra of the two diacetates were identical.

Following a mixed fraction (1 g), the slower-moving component was eluted as a syrup (3 g) contaminated with a small amount of ethane-1,2-diol. Conventional treatment of this product (2.2 g) with sodium acetate–acetic anhydride gave syrupy methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranoside (0.65 g), $[\alpha]_D^{30}$ +113° (Found: C, 48.1; H, 5.5; F, 6.0. $C_{13}H_{19}FO_8$ calc.: C, 48.4; H, 5.9; F, 5.9%).

Deacetylation of the foregoing compound with methanolic ammonia, in the usual manner, gave methyl 6-deoxy-6-fluoro-α-D-glucopyranoside, m.p. 103–105°, $[\alpha]_D^{30}$ +167° (water): lit.[5] m.p. 109–110°, $[\alpha]_D$ +43° (water).

1,2-O-Isopropylidene-6-O-mesyl-α-D-glucofuranose (2). — Anhydrous D-glucose (100 g) and boric acid (35 g) were stirred with a solution of conc. sulphuric acid (41.6 ml) in acetone (1.25 l) for 4.5 h at room temperature. Pyridine (120 ml) was then added to the cooled (~0°) mixture and, after a few minutes, the supernatant was decanted and stirred overnight with anhydrous potassium carbonate (40 g). The filtered mixture was concentrated at 40°/~12 mmHg, and a cold (*ca.* −5°) solution of the syrupy residue in pyridine (300 ml) was treated with mesyl chloride (100 ml) portion-wise during 2 h whilst the temperature of the mixture was maintained at 0–5°. After subsequent stirring overnight at room temperature, the mixture was filtered, diluted with water (200 ml), and concentrated at 50°/~12 mmHg. The residue was treated with water (500 ml) and extracted with ethyl acetate (3 × 500 ml). The combined extracts were concentrated (to 200 ml), added to a column (50 × 4 cm) of Kieselgel, and eluted with ether. Concentration of the appropriate fractions gave the title compound (60.5 g, 35%), m.p. 92° (from chloroform); lit.[7] m.p. 99°.

Methanesulphonate displacements. — A solution of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-mesyl-α-D-glucofuranose[4] (9 g) and lithium chloride (10 g) in *N,N*-dimethylformamide[27] (200 ml) was heated to the boiling point and then allowed to cool. Dilution of the solution with water (400 ml), followed by collection of the product and recrystallisation from methanol (70 ml), gave 3,5-*O*-benzylidene-6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (5.4 g, 65%), m.p. 114–115°, $[\alpha]_D^{30}$ +18° (Found: C, 58.7; H, 5.7; Cl, 10.6. $C_{16}H_{19}ClO_5$ calc.: C, 58.8; H, 5.9; Cl, 10.9%).

In a similar experiment, but using lithium bromide (10 g), 3,5-*O*-benzylidene-6-bromo-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (40%) was obtained having m.p. 114–115°, $[\alpha]_D^{30}$ +16° (Found: C, 51.8; H, 4.9; Br, 21.8. $C_{16}H_{19}BrO_5$ calc.: C, 51.8; H, 5.2; Br, 21.5%).

Resin hydrolyses[9]. — An aqueous, ethanolic solution–suspension of the above bromobenzylidene compound was heated at 70° for 4 h in the presence of Amberlite

IR-120 (H^+) resin. Concentration of the filtered hydrolysate and elution of the residue from Kieselgel with ethyl acetate gave 6-bromo-6-deoxy-D-glucose (65%), m.p. 129–130° (decomp.; from ethyl acetate), $[\alpha]_D^{30}$ +82 (2 min) → +45° (equil., water); lit.[27] $[\alpha]_D$ +43° (Found: C, 30.1; H, 4.2; Br, 33.2. $C_6H_{11}BrO_5$ calc.: C, 29.6; H, 4.6; Br, 32.9%).

Resin hydrolysis of 6-bromo-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[28] gave 6-bromo-6-deoxy-D-galactose (65%), m.p. 95–97° (from ethyl acetate), $[\alpha]_D$ +74° (equil., water): lit.[27] $[\alpha]_D$ +56° (water) (Found: C, 30.0; H, 4.4; Br, 33.3%).

Resin hydrolysis (5 h, 70°) of 3,5-*O*-benzylidene-6-deoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose gave 6-deoxy-6-fluoro-α-D-glucose (86%), m.p. 152° (from ethyl acetate–ethanol), $[\alpha]_D$ +92 (2 min) → +47° (equil., water); lit.[4] m.p. 155°, $[\alpha]_D$ +85.8 → +46.8°.

Tetra-acetates of 6-deoxy-6-fluoro-D-glucopyranose. — A solution of the αβ-tetra-acetate (0.5 g), obtained by treatment of 6-deoxy-6-fluoro-D-glucose with pyridine–acetic anhydride at room temperature in the usual manner, in acetic anhydride (2 ml) containing fused zinc chloride (0.15 g) was heated at 100° for 3 h. The mixture was then concentrated at 30°/1 mmHg, and the residue was eluted from Kieselgel with ether–light petroleum (b.p. 40–60°) (2:1) to give crude α-tetra-acetate (**5**, 0.49 g). Recrystallisation from benzene–light petroleum gave material (0.32 g) having m.p. 128–129°, $[\alpha]_D^{30}$ +107° (Found: C, 47.9; H, 5.3; F, 5.5. $C_{14}H_{19}FO_9$ calc.: C, 48.0; H, 5.5; F, 5.4%).

6-Deoxy-6-fluoro-D-glucose (0.2 g) was treated with a boiling solution of sodium acetate (0.3 g) in acetic anhydride (0.4 ml) for 0.4 h. The crude product, isolated in the usual manner, was eluted from Kieselgel with ether–light petroleum (2:1) to give material (0.35 g) which was recrystallised from benzene–light petroleum to give the β-tetra-acetate **6**, m.p. 123–124°, $[\alpha]_D^{30}$ +21.5°; lit.[4] m.p. 125–126°, $[\alpha]_D$ +20.1° (pyridine).

2,3,4-Tri-O-acetyl-6-deoxy-6-fluoro-α-(**7**) *and -β-D-glucopyranosyl fluorides* (**8**). — (*a*) The foregoing αβ-tetra-acetate (2.5 g) was treated with anhydrous hydrogen fluoride (20 ml) at *ca.* −10° for 20 min. After a further 15 min at room temperature, the mixture was poured into water (100 ml). Extraction with chloroform, in the usual manner after neutralisation, gave a product containing four components (R_F 0.2, 0.35, 0.4, and 0.6; t.l.c., ether–light petroleum, 3:1).

Elution of the mixture from Kieselgel (200 g) with ether–light petroleum (2:1) gave, in order of elution, (*1*) the product (0.68 g) of R_F 0.6, which was recrystallised from the same solvent mixture to give 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl fluoride (**7**, 0.6 g), m.p. 106–106.5°, $[\alpha]_D^{30}$ +106° (Found: C, 46.6; H, 5.2; F, 12.4. $C_{12}H_{16}F_2O_7$ calc.: C, 46.4; H, 5.2; F, 12.3%). (*2*) An unidentified product (0.11 g), R_F 0.4. (*3*) Material (0.72 g) having R_F 0.35 which was recrystallised from benzene–light petroleum to give 3,4-di-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl fluoride (**9**), m.p. 126–127°, $[\alpha]_D^{30}$ +131° (Found: C, 44.6; H, 5.8; F, 14.4. $C_{10}H_{14}F_2O_6$ calc.: C, 44.8; H, 5.3; F, 14.2%). (*4*) An unidentified product (50 mg), R_F 0.2.

Treatment of **9** with acetic anhydride–pyridine, in the usual manner, gave **7**, m.p. 105–106° alone or in admixture with the product described above.

(*b*) On dissolution of the αβ-tetra-acetate (0.95 g) described above in a 45% solution (4 ml) of hydrogen bromide in acetic acid at room temperature, reaction was complete in 1.2 h [t.l.c., ether–light petroleum (b.p. 40–60°), 1:1] to give a single product having R_F 0.4. Concentration of the reaction mixture at 30°/0.5 mmHg gave 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl bromide[4] (1 g) as an unstable, crystalline product, a portion of which (0.9 g) was dissolved in acetonitrile (10 ml) and stirred with silver fluoride (1.5 g) at room temperature. After 1 h, reaction was complete [t.l.c., ether–light petroleum (b.p. 40–60°), 1:1]. The filtered mixture was concentrated, and the residue was eluted from Kieselgel with ether–light petroleum (2:1). Recrystallisation of the product from benzene–light petroleum gave **8** (0.58 g), m.p. 141–142°, $[\alpha]_D^{30}$ +20° (Found: C, 46.3; H, 5.3; F, 12.2. $C_{12}H_{16}F_2O_7$ calc.: C, 46.4; H, 5.2; F, 12.3%).

6-Deoxy-6-fluoro-α-(**12**) *and -β-*D*-glucopyranosyl fluoride* (**13**). — When the triacetate **7** (0.35 g) was dissolved in a saturated solution (25 ml) of methanolic ammonia at room temperature, monitoring by t.l.c. (ethyl acetate) indicated that deacetylation was complete in 30 min. Concentration of the solution and recrystallisation of the residue from ethyl acetate gave the α-difluoride **12** (0.1 g), m.p. 130–131°, $[\alpha]_D^{30}$ +95° (*c* 1, water) (Found: C, 39.4; H, 5.7; F, 20.9. $C_6H_{10}F_2O_4$ calc.: C, 39.1; H, 5.5; F, 20.6%),

Similarly, deacetylation of the triacetate **8** (0.3 g) gave the β-difluoride **13** (0.12 g), m.p. 139–140° (decomp.) (from ethyl acetate), $[\alpha]_D^{30}$ +20° (*c* 1, methanol) (Found: C, 39.4; H, 5.2; F, 21.0%).

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