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FLUORINATED CARBOHYDRATES

PART I. 3-DEOXY-3-FLUORO-D-GLUCOSE[1]

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INTRODUCTION

The knowledge[2] that replacement of hydrogen atoms or functional groups in an organic compound by fluorine atoms may cause a dramatic change in biological activity is undoubtedly one reason for interest in the synthesis of deoxyfluoro sugars*. Until recently and in spite of considerable efforts[3], deoxyfluoro sugars, as a class of carbohydrate derivative, were poorly exemplified, and, in the case of secondary fluorides having the *gluco* configuration, they are still relatively inaccessible synthetically.

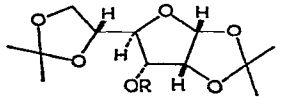
Primary deoxyfluoro sugars are readily obtained by nucleophilic displacement of suitably substituted sugar derivatives by fluoride salts in such solvents as ethylene glycol. In this way, derivatives of 6-deoxy-6-fluoro-D-galactose[4,5], 6-deoxy-6-fluoro-D-glucose[6], and 5-deoxy-5-fluoro-D-ribose[4] have been prepared. The only examples of carbohydrate geminal difluorides, 2,5-anhydro-1-deoxy-1,1-difluoro-D-ribitol and 2,5-anhydro-1-deoxy-1,1-difluoro-D-mannitol, were obtained by treatment of 3,4-di-*O*-acetyl-D-arabinal and 3,4,6-tri-*O*-acetyl-D-glucal with lead tetra-acetate–hydrogen fluoride followed by de-acetylation[7].

There have been several approaches to the synthesis of carbohydrate secondary fluorides. Total synthesis from simple aliphatic precursors has given (±)-2-deoxy-2-fluoroglyceraldehyde[3,8] and 2-deoxy-2-fluoro-DL-ribitol[9], but this approach is limited because of the formation of racemic products. The cleavage of suitably protected sugar epoxides with hydrogen fluoride has permitted the synthesis of 3-deoxy-3-fluoro-L-xylose[10a] (hydrogen fluoride–*p*-dioxane at 120°), 3-deoxy-3-fluoro-D-arabinose[10b] (potassium hydrogen fluoride in ethylene glycol), 3-deoxy-3-fluoro-D-xylose[11], (potassium hydrogen fluoride–diethylene glycol, potassium fluoride–molten acetamide), and 2-deoxy-2-fluoro-D-altrose and 3-deoxy-3-fluoro-D-glucose[12] (hydrogen fluoride–boron trifluoride at −70°). 3-Deoxy-3-fluoro-D-xylose has been converted into the D-arabinose and D-ribose analogues[11], and 2-deoxy-2-fluoro-D-allose has been

*The term deoxyfluoro sugars connotes carbohydrates in which one or more of the hydroxyl functions, other than the glycosidic centre [glycosyl fluorides, see F. Micheel and A. Klemer, *Advan. Carbohydrate Chem.*, 16 (1961) 85], have been replaced by a fluorine atom.

obtained by epimerisation[12] of the D-altrose analogue. Syntheses of 2-deoxy-2-fluorouridine[13] and 2-deoxy-2-fluorothymidine[14] have been described, and from the former compound, 2-deoxy-2-fluoro-D-ribose has been obtained[15].

Several methods that have been used successfully in the synthesis of aliphatic secondary fluorides failed when applied in the carbohydrate field[16]. Although direct displacement of carbohydrate primary sulphonates with fluoride ion proceeds readily[4], the method has not been successfully applied to secondary sulphonates[5]. Because of solvation, fluoride ion in a protic solvent is a relatively poor nucleophile, but, in dipolar aprotic solvents, only cations are strongly solvated[17], and the nucleophilicity of fluoride ion is significantly enhanced. Thus, Henbest and Jackson[18] have shown that sulphonates attached to five-membered carbocyclic compounds (testosterone toluene-*p*-sulphonate) and axially or equatorially to six-membered rings (cholestan-3-α- and 3-β-yl toluene-*p*-sulphonate) can be converted into fluorides, in good yield with inversion of configuration, by treatment with tetrabutylammonium fluoride in acetone or ethyl methyl ketone. In seeking new routes to deoxyfluoro derivatives of D-glucose, we were thus prompted to examine the response of sulphonates of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (*e.g.*, **1**) towards tetra-alkylammonium fluorides in dipolar aprotic solvents. 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose[19] (**2**) is now readily[19–21] available, and it appeared from molecular models that, in a nucleophilic displacement of a 3-sulphonate group, the attack of fluoride ion would be from the *exo*-side of the *cis*-fused tri-oxabicyclo[3.3.0]octane ring-system formed by the tetrahydrofuran ring and the 1,2-*O*-isopropylidene group, and steric hindrance would be minimal. The opposite situation obtains for 3-sulphonates of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which are strongly resistant towards attack by nucleophiles[22].



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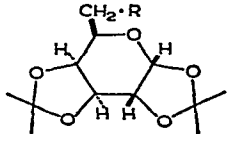
2,R = H

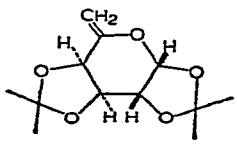


3, R = OTs
4, R = F

1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (**2**) was prepared by oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with phosphorus pentaoxide in methyl sulphoxide[20], followed by reduction of the resulting ketone with sodium borohydride[19]. A lower yield of ketone was obtained with methyl sulphoxide–acetic anhydride[21], but this reagent was more convenient to use. Sulphonylation of the allose derivative (**2**) proceeded readily on treatment with toluene-*p*-sulphonyl chloride in pyridine at room temperature.

In preliminary experiments, 1,2:3,4-di-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactopyranose (**3**) was used as a model compound and was treated with tetrabutylammonium fluoride variously in ethylene glycol (reaction temperature, 100°), tetrahydrofuran (80°), acetone (56°), *N*,*N*-dimethylformamide (37°, 50–60°), and acetonitrile (37°, 63–67°, 81–83°). Surprisingly, no reaction occurred in ethylene glycol

after 22 h, but, in all other cases, a mixture of products was obtained which contained components having retention times in gas–liquid chromatography identical with those of 6-deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[4] (**4**) and 6-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*arabino*-hex-5-enopyranose[23a] (**5**). In those cases where reaction temperature was varied, the proportion of olefin (**5**) in the product mixture was higher at the elevated temperature; the fluoro derivative (**4**) was stable under the reaction conditions. Acetonitrile appeared to be the most suitable solvent; thus, after reaction for 10 h at 81–83° with a six-fold excess of tetrabutylammonium fluoride, the yield of fluoride **4** was 69%, and the ratio of olefin to fluoride was *ca.* 1:2.2.



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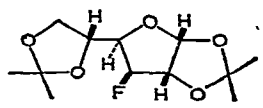

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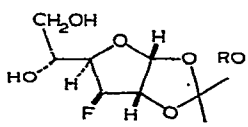
1,2:5,6-Di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose (**1**) reacted slowly with tetrabutylammonium fluoride in acetonitrile at 70–80° (completion of reaction required 3.5 days), but 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) was subsequently isolated in 74% yield after column chromatography and distillation. Under essentially similar conditions of reaction, 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose gave 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose[23b] (**10**) as the preponderant product. Thus, in devising syntheses of carbohydrate secondary fluorides based on fluoride displacements, careful attention must be paid to the steric environment of the carbon atom carrying the leaving group. Other examples of fluoride displacements are being studied.



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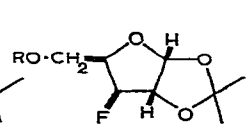
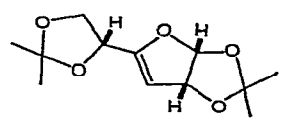


8, R = H
9, R = Ts



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On mechanistic grounds and by analogy, compound **6** would be expected to have the D-*gluco* configuration. Thus, the toluene-*p*-sulphonate **1** reacts with sodium azide in *N*,*N*-dimethylformamide to give 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[24]. The ^{19}F n.m.r. spectrum (Perkin–Elmer R-10, $CDCl_3$) of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which was consistent with the assigned structure, contained 8 signals (centre-of-gravity ∅, +207.8 p.p.m. with respect to CCl_3F) having the following coupling constants J_{H_3F} 49.8, J_{H_4F} 29.8, and J_{H_2F} 10.8 Hz. The ^1H-spectrum ($CHCl_3$, internal tetramethylsilane)

showed, *inter alia*, a doublet at τ 4.06 (J 3.8 Hz) for the anomeric proton, and the low-field part of the signal for H-3 appeared at τ 4.60.*

The D-*gluco* configuration of compound **6** was established unequivocally by the following sequence of reactions. Graded hydrolysis of compound **6** with sulphuric acid in *p*-dioxane–methanol cleaved the 5,6-acetal group and gave syrupy 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**) which was characterised as the 5,6-benzeneboronate and the 5,6-carbonate. Treatment of the diol (**7**), in sequence, with sodium periodate and sodium borohydride gave syrupy 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-xylofuranose (**8**) which was characterised as the 5-toluene-*p*-sulphonate (**9**). Acidic hydrolysis of compound **8** afforded 3-deoxy-3-fluoro-D-xylose, which was identical with the authentic compound[11], and the derived 2,6-dichlorophenylhydrazone was identical with the compound reported by Taylor *et al.*[10b]. The establishment of the D-*xylo* configuration for compound **8** requires that compound **6** has the D-*gluco* configuration.

Hydrolysis of compound **6** with hot N sulphuric acid or, preferably, with a hot, aqueous suspension of Amberlite IR-120 (H^+) gave 3-deoxy-3-fluoro-D-glucose. This was non-crystalline but was homogeneous in paper chromatography, and its mobility and detection characteristics were identical with those of the authentic compound described by Johansson and Lindberg[12]. 3-Deoxy-3-fluoro-D-glucose gave a crystalline β-tetra-acetate on treatment with sodium acetate and hot acetic anhydride. The stability of the fluorine atom under other reaction conditions common in carbohydrate chemistry was exemplified by the fact that acid-catalysed acetonation of 3-deoxy-3-fluoro-D-glucose, followed by graded acidic hydrolysis of the resulting diacetal, gave 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**). When a similar reaction sequence was performed with cyclohexanone, a mono-acetal was obtained, which is provisionally assigned the structure 1,2-*O*-cyclohexylidene-3-deoxy-3-fluoro-α-D-glucofuranose.

The yields in the conversion[19–21] of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose into the D-allose isomer (**2**) and in the various stages of the subsequent reaction sequence **2**→**1**→**6**→3-deoxy-3-fluoro-D-glucose are uniformly high (overall yield from D-glucose, 15–18%), and the route provides a more ready access to the final product than does the original method[12]. The key stages in the latter route involved treatment of methyl 2,3-anhydro-4,6-di-*O*-methyl-α-D-allopyranoside with boron trifluoride–hydrogen fluoride at −70° to give mainly 2-deoxy-2-fluoro-4,6-di-*O*-methyl-D-altropyranosyl fluoride, together with a small proportion of 3-deoxy-3-fluoro-4,6-di-*O*-methyl-D-glucopyranosyl fluoride, from which the deoxyfluoro sugars were subsequently obtained.

The biological properties of 3-deoxy-3-fluoro-D-xylose and 3-deoxy-3-fluoro-D-glucose are being investigated and will be reported elsewhere.

*A detailed analysis of the n.m.r. spectra of the fluorine-containing sugar derivatives described in this paper will be published elsewhere.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) was performed on glass plates (3.25 in sq.) with Kieselgel G (Merck, 7731) and detection with iodine vapour or conc. sulphuric acid.

Treatment of 1,2:3,4-di-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-galactopyranose with fluoride. — A solution of the title compound (**3**, 0.5 g) and tetrabutylammonium fluoride (2 g, *ca.* 6 mol.) in acetonitrile (2 ml) was boiled under reflux, and monitored by t.l.c. (carbon tetrachloride–ether, 9:1). After 10 h, reaction was complete, and a product having an R_F value identical with that of 6-deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[4] was detected. The mixture was diluted with water and extracted with ether in the usual manner. The combined and dried ($MgSO_4$) extracts were concentrated, and the residue was distilled to give a product (0.32 g), b.p. 95–140° (bath)/0.1 mm, ν_{max}^{liquid} 1660 cm^{-1} (C=C), which, on examination by g.l.c. [Pye-Argon chromatograph, poly(ethyleneglycol adipate) on Celite, 150°], showed two components, with retention times of *ca.* 15 and 19 min, corresponding to the olefin **5** and the fluoride **4**.

A series of experiments was then carried out with variation of solvents, temperature, and reaction time. The products were isolated essentially as described above and analysed by g.l.c. by comparison with mixtures, of known composition, containing compounds **4** and **5**. The results are shown in Table I.

TABLE I

TREATMENT OF 1,2:3,4-DI-*O*-ISOPROPYLIDENE-6-*O*-TOLUENE-*p*-SULPHONYL-α-D-GALACTOPYRANOSE WITH TETRABUTYLAMMONIUM FLUORIDE

Solvent	*Temp. (degrees)*	*Reaction time*	*Molar excess of Bu_4NF*	*Ratio of fluoride (4): olefin (5)*	*Yield of fluoride 4 (%)*
Ethylene glycol	100	22 h	5	No reaction	No reaction
Tetrahydrofuran	80	24 h	5	1.4:1	29
Acetone	56	16 h	9	1.6:1	[a]
Acetonitrile	81–83	10 h	6	2.2:1	69
	63–67	3.5 days	9	3.7:1	61
	37	9 days	6	5.5:1	39
	37	23 days	15	3.2:1	64
N,N-Dimethylformamide	50–60	3.5 days	6	3.2:1	53
	37	13.5 days	6	3.0:1	45

[a]Additional products formed.

A mixture of 6-deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.17 g), tetrabutylammonium fluoride (2 g), and acetonitrile (2 ml) was stored for 11 days at 37°. The mixture was then processed as described above, and the product was examined by g.l.c.; no trace of the olefin **5** could be detected.

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose. — 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose[19,20] [7.7 g, m.p. 74–75°, $[\alpha]_D$ +37° (chloroform)]

was sulphonylated in the usual manner with toluene-*p*-sulphonyl chloride (7.7 g, 1.24 mol.) and pyridine (77 ml, dried by repeated distillation from phosphorus pentaoxide) for 21 h at room temperature. Ice–water (10 ml) was added, and, after a few min, the mixture was poured into ice–water (1.5 l). Recrystallisation of the product from ethanol–hexane yielded the title compound (8.8 g, 72%), m.p. 120–121°, $[\alpha]_D$ +87° (*c* 1.0, chloroform) (Found: C, 54.75; H, 6.3; S, 8.0. $C_{19}H_{26}O_8S$ calc.: C, 55.1; H, 6.3; S, 7.7%).

*3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose.* — Tetrabutylammonium fluoride[25] was prepared by titration of 40% aqueous tetrabutylammonium hydroxide with 20% aqueous hydrofluoric acid to pH 7. The solution was concentrated under reduced pressure, and the resulting syrup was dried and stored over phosphorus pentaoxide at 0.1 mm. Dehydration of the fluoride by prolonged azeotropic distillation with benzene causes decomposition.

A mixture of 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose (40 g), tetrabutylammonium fluoride (136 g, 5.4 mol.), and acetonitrile (200 ml, distilled from phosphorus pentaoxide) was kept under reflux at 70–80°, and monitored by t.l.c. (benzene–ether, 9:1). After 3.5 days, reaction appeared to be complete, and the mixture was poured into ether (500 ml) and washed with water (2 × 200 ml). The ethereal layer was dried ($MgSO_4$), and concentrated under diminished pressure, and the syrupy residue was submitted to column chromatography on silica gel (Hopkin & Williams). Elution with benzene–ether (9:1) yielded 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (18.4 g, 71%), b.p. 66–70°/0.03 mm, $[\alpha]_D^{30}$ −22° (*c* 1, chloroform) (Found: C, 55.5; H, 7.3; F, 7.6. $C_{12}H_{19}FO_5$ calc.: C, 55.0; H, 7.3; F, 7.3%).

3-Deoxy-3-fluoro-D-glucose. — 3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1 g) was heated under reflux with N sulphuric acid (50 ml) for 1 h; t.l.c. then showed reaction to be complete. The hydrolysate was neutralised ($BaCO_3$), and concentrated under diminished pressure, and the residue was eluted from Kieselgel (Merck, 7734) with ethyl acetate–ethanol (9:1) to yield syrupy, chromatographically homogeneous 3-deoxy-3-fluoro-D-glucose (0.4 g, 57%), $[\alpha]_D$ +47° (*c* 0.7, water), R_F 0.4 (t.l.c., ethyl acetate–ethanol, 4:1) and R_G 2.1 (chromatography on Whatman No. 1 paper, organic phase of butanol–ethanol–water, 4:1:5). The mobility in paper chromatography and response to aniline hydrogen phthalate[26] were identical with those of 3-deoxy-3-fluoro-D-glucose described by Johansson and Lindberg[12].

An alternative and more convenient procedure for hydrolysis was as follows. A solution of the diacetal (1.2 g) in ethanol (10 ml) and water (50 ml) was stirred at 60–70° with Amberlite IR-120 (H^+, *ca.* 15 ml). The hydrolysis was monitored by t.l.c. (ethyl acetate) and shown to be complete in 8 h. Concentration of the filtered solution gave chromatographically homogeneous 3-deoxy-3-fluoro-D-glucose (0.8 g, 96%). The foregoing product (0.39 g) was treated with a boiling solution of sodium acetate (0.5 g) in acetic anhydride (7 ml) for 10 min. The product, isolated in the usual manner[27], was twice recrystallised from benzene–light petroleum (b.p. 60–80°) to give 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-β-D-glucose, m.p. 119–120°, $[\alpha]_D^{20}$ −12°

(*c* 0.9, chloroform) (Found: C, 48.2; H, 5.4; F, 5.4. $C_{14}H_{19}FO_9$ calc.: C, 48.0; H, 5.4; F, 5.4%).

1,2-O-Cyclohexylidene-3-deoxy-3-fluoro-α-D-glucofuranose. — A mixture of 3-deoxy-3-fluoro-D-glucose (0.3 g), cyclohexanone (5 ml), and conc. sulphuric acid (0.25 ml) was stored at room temperature and monitored by t.l.c.; reaction was complete in 12 h. The mixture was extracted with heptane (10 ml), and the extract was concentrated under diminished pressure. The residue was subjected to graded hydrolysis by treatment with *p*-dioxane–methanol–5N sulphuric acid (6:3:1, 10 ml) for 5 h at room temperature and then neutralised with barium carbonate. The hydrolysate was concentrated under diminished pressure, and the residue was chromatographed on Kieselgel (Merck, 7734). Elution with benzene–methanol (9:1) yielded the title compound (0.25 g, 58%), m.p. 121–122° [from ethanol–light petroleum (b.p. 60–80°)], $[\alpha]_D^{25}$ −12° (*c* 0.7, chloroform) (Found: C, 54.9; H, 7.4; F, 7.3. $C_{12}H_{19}FO_5$ calc.: C, 55.0; H, 7.25; F, 7.3%).

3-Deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucose. — (*a*) A solution of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucose (4.45 g) in *p*-dioxane–methanol–5N sulphuric acid (6:3:1, 126 ml) was stored at room temperature and monitored by t.l.c. (benzene–ether, 9:1). After 4 h, no starting material remained. The hydrolysate was neutralised ($BaCO_3$), and concentrated under diminished pressure, and the residue was distilled to yield 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (3.77 g, 83%), b.p. 124–126°/0.3–0.4 mm, m.p. 50–52° [from toluene–light petroleum (b.p. 60–80°)], $[\alpha]_D$ −18° (*c* 0.8, chloroform) (Found: C, 48.4; H, 7.0. $C_9H_{15}FO_5$ calc.: C, 48.6; H, 6.8%).

(*b*) A mixture of 3-deoxy-3-fluoro-D-glucose (0.5 g), dry acetone (20 ml), and conc. sulphuric acid (0.8 ml) was stored at room temperature; reaction appeared to be complete in 20 h (t.l.c.). The mixture was neutralised (K_2CO_3) and concentrated, and the syrupy residue was subjected to graded hydrolysis by storage at room temperature for 4 h with *p*-dioxane–methanol–5N sulphuric acid (6:3:1, 15 ml). After neutralisation ($BaCO_3$), and concentration under diminished pressure, the residue was eluted from Kieselgel (35 g, Merck, 7734) with benzene–methanol (9:1) to yield 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (0.38 g, 62%), m.p. 51–52° alone or in admixture with the product described in (*a*).

3-Deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose 5,6-benzeneboronate. — 3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (159 mg), benzeneboronic acid (87.5 mg, 1 mol.), and benzene (50 ml) were refluxed for 2 h in a Dean & Stark apparatus. Evaporation of the benzene, followed by recrystallisation of the product from light petroleum (b.p. 40–60°), yielded the title compound (150 mg, 68%), m.p. 115–116°, $[\alpha]_D$ −2° (*c* 2.1, chloroform) (Found: C, 58.2; H, 5.7; F, 6.4. $C_{15}H_{18}BFO_5$ calc.: C, 58.5; H, 5.8; F, 6.2%).

3-Deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose 5,6-carbonate. — Phosgene was bubbled for 1 h through a solution of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (300 mg) in pyridine (15 ml) at 0°. Excess of phosgene was then destroyed with water (50 ml), the mixture was extracted with chloroform

(3 × 50 ml), and the combined extracts were dried ($MgSO_4$) and concentrated. Recrystallisation of the residue from ethanol–light petroleum (b.p. 60–80°) gave the title compound (300 mg, 90%), m.p. 84–85°, $[\alpha]_D^{25}$ −27° (*c* 1.0, chloroform) (Found: C, 48.7; H, 5.5; F, 8.0. $C_{10}H_{13}FO_6$ calc.: C, 48.4; H, 5.2; F, 7.7%).

3-Deoxy-3-fluoro-1,2-O-isopropylidene-α-D-xylofuranose. — To a solution of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (6.5 g) and sodium hydrogen carbonate (2 g) in water (50 ml) was added sodium metaperiodate (8 g), portionwise with stirring during 1 h. After addition of excess of barium chloride solution and barium carbonate, the filtered solution was treated portionwise with sodium borohydride (10 g). After 1 h, the solution was extracted with chloroform (4 × 50 ml), the combined extracts were dried ($MgSO_4$), and concentrated under diminished pressure, and the residue was distilled to give 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-xylofuranose (4.0 g, 71%), b.p. 95°/3–4 mm, $[\alpha]_D^{20}$ −20° (*c* 1.0, chloroform) (Found: C, 49.8; H, 6.8. $C_8H_{13}FO_4$ calc.: C, 50.0; H, 6.8%).

The toluene-*p*-sulphonate, prepared in the usual manner, had m.p. 60–61°, [from ethanol–light petroleum (b.p. 40–60°)], $[\alpha]_D$ −27° (*c* 2, chloroform) (Found: C, 52.1; H, 5.7; F, 5.7. $C_{15}H_{19}FO_6S$ calc.: C, 52.0; H, 5.5; F, 5.5%).

3-Deoxy-3-fluoro-D-xylose. — 3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-xylofuranose (1 g) was heated under reflux with N sulphuric acid (25 ml) for 1 h. The cooled solution was neutralised ($BaCO_3$), and concentrated under diminished pressure. The residue was eluted from Kieselgel (Merck, 7734) with ethyl acetate, to give a chromatographically homogeneous syrup (0.53 g, 67%) that crystallised on seeding. Recrystallisation from ethanol gave 3-deoxy-3-fluoro-D-xylose, m.p. 134–136°, $[\alpha]_D^{20}$ +37° (*c* 0.3, water, equil.); lit.[11], m.p. 125–127°, $[\alpha]_D^{25}$ +70 → +38° (water). The i.r. spectra (Nujol) of the compounds were indistinguishable.

3-Deoxy-3-fluoro-D-xylose (100 mg) and 2,5-dichlorophenylhydrazine (130 mg) were dissolved in methanol (50 ml), and the solution was concentrated using a steam bath. Chromatography of the residue on Kieselgel (25 g, Merck, 7734), with elution by ethyl acetate, yielded the chromatographically homogeneous 2,5-dichlorophenylhydrazone, m.p. 64–66° (from methanol–water). A sample of the 2,5-dichlorophenylhydrazone[10b], kindly provided by Dr. N. F. Taylor and which had partially decomposed on storage, was purified by chromatography and recrystallised from methanol–water to give a product having m.p. 64–67°, alone or in admixture with the product described above. The i.r. spectra (Nujol) of the two 2,5-dichlorophenylhydrazones were indistinguishable. The 2,5-dichlorophenylhydrazone underwent partial decomposition on storage at room temperature for a few days.

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SUMMARY

Treatment of 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-allofuranose with tetrabutylammonium fluoride in acetonitrile gave 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) in 74% yield. The structure of **6** was established by a multistage conversion into known 3-deoxy-3-fluoro-D-xylose. Graded hydrolysis of **6** with acid gave 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**), and total hydrolysis gave 3-deoxy-3-fluoro-D-glucose (15–18% overall yield from D-glucose).

3-Deoxy-3-fluoro-D-glucose gave a crystalline β-tetra-acetate and was reconverted into **7** on treatment with acetone in the presence of acid, followed by graded hydrolysis with acid. In a similar manner, 1,2-*O*-cyclohexylidene-3-deoxy-3-fluoro-α-D-glucofuranose was obtained.

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