Preliminary communication

2-Deoxy-2,2-difluoro-D-*arabino*-hexose ("2,2-difluoroglucose")

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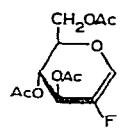
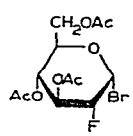
Of the series of fluorinated derivatives of D-glucopyranose required for a study[1] of the structure–activity relationship for substrates of the hexokinase isozymes of normal and cancerous tissue[2], all the monofluoro derivatives have now been described[3]. As HO-2, apparently, is not critically involved[4] in the D-glucose–hexokinase complex, 2-deoxy-2-fluoro-D-mannose[5] and 2-deoxy-2,2-difluoro-D-*arabino*-hexose (8, "2,2-difluoroglucose") are also of particular interest. We now report on the latter compound.

An obvious approach to the difluoride 8 is by way of the addition of trifluoromethyl hypofluorite to 3,4,6-tri-*O*-acetyl-2-fluoro-D-glucal (**1**). Conventional treatment with hydrogen bromide of the α,β mixture of tetraacetates formed from 2-deoxy-2-fluoro-D-glucose[5] and pyridine–acetic anhydride gave 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (**2**), m.p. 79–80° (from ether), $[\alpha]_D$ +229° (unless stated otherwise, $[\alpha]_D$ values are for 1–2% solutions in chloroform), $J_{1,2}$ 3, $J_{F,1} < 0.5$ Hz (~10% solution in $CDCl_3$) (Found: C, 38.9; H, 4.4; Br, 21.3; F, 5.1. $C_{12}H_{16}BrFO_7$ calc.: C, 38.8; H, 4.3; Br, 21.6; F, 5.1%). With boiling acetonitrile–triethylamine, 2 gave the fluoroglucal **1**, b.p. 95°/0.04 torr, $[\alpha]_D$ −1° (Found: C, 49.7; H, 5.5; F, 6.5. $C_{12}H_{15}FO_7$ calc.: C, 49.6; H, 5.2; F, 6.55%).



1



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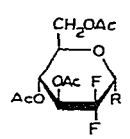

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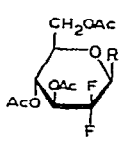
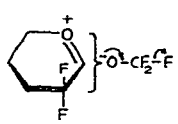
4, R = F



5, R = OCF_3
6, R = F



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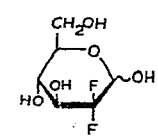

8

Treatment[5] of **1** with trifluorofluoroxymethane at ~−80° gave, in order of elution from Kieselgel 7734 (Merck), trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2,2-difluoro-α-D-*arabino*-hexopyranoside (**3**), yield 8.5%, m.p. 77–78°, $[\alpha]_D$ +104° (Found: C, 39.5; H, 3.9; F, 24.35. $C_{13}H_{15}F_5O_8$ calc.: C, 39.6; H, 3.8; F, 24.1%), 3,4,6-tri-*O*-acetyl-2-deoxy-2,2-difluoro-α-D-*arabino*-hexosyl fluoride (**4**), yield ~50%, m.p. 81–84°, $[\alpha]_D$ +172°, trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2,2-difluoro-β-D-*arabino*-hexopyranoside (**5**), yield 2%, m.p. 55–56°, $[\alpha]_D$ +22.5° (Found: C, 39.6; H, 3.7; F, 24.1%), and 3,4,6-tri-*O*-acetyl-2-deoxy-2,2-difluoro-β-D-*arabino*-hexopyranosyl fluoride (**6**), yield 16%, m.p. 67°, $[\alpha]_D$ +46° (Found: C, 44.2; H, 4.7; F, 17.75. $C_{12}H_{15}F_3O_7$ calc.: C, 43.9; H, 4.6; F, 17.4%). Satisfactory elemental analytical data could not be obtained for **4**,although the presence of three fluorine substituents was confirmed by n.m.r. spectroscopy and the compound gave a molecular ion in mass spectrometry (*m/e* 328, MS-12, 70 eV, source temperature 85°) as did the isomeric trifluoride **6**.

Trifluorofluoroxymethane adds *cis* to the double bond in both 3,4,6-tri-*O*-acetyl-D-glucal[5] and its 2-fluoro derivative **1**, on the side remote from AcO-3. However, for the former compound, the trifluoromethyl α-D-glycoside is the preponderant product, whereas the α-D-glycosyl fluoride is the major product from the fluoroglucal. Presumably[6], in the latter reaction, the 2,2-difluorooxonium ion **7** is more stable than the analogue bearing one fluorine substituent on C-2. A greater loss of COF_2 from the initial counter-ion (CF_3O^-) of the intermediate ion-pair is thereby facilitated, with a consequent increase in the proportion of glycosyl fluorides in the product mixture.

Hydrolysis of **3** with boiling 2M hydrochloric acid or 3M sulphuric acid for 3 h gave mainly 2-deoxy-2,2-difluoro-D-*arabino*-hexose (**8**), together with traces of 2-deoxy-2-fluoro-D-glucose and/or 2-deoxy-2-fluoro-D-mannose (*cf.* Ref. 1), as shown by g.l.c. [Pye 104 chromatograph, 17% poly(ethylene glycol succinate) on Gas-Chrom P (100–200 mesh), 130°] after trimethylsilylation[7]. After purification by elution from Kieselgel with ethyl acetate, the difluoro sugar **8** had m.p. 167–168°, $[\alpha]_D$ +29° (4 min) → +57.5° (equil., water) (Found: C, 35.8; H, 4.8; F, 18.7. $C_6H_{10}F_2O_5$ calc.: C, 36.0; H, 5.0; F, 19.0%). The n.m.r. spectrum of an ~10% solution of **8** in methyl sulphoxide-d_6 showed the following ^{19}F resonances (downfield with respect to external C_6F_6): α-D anomer, F_e 4152 Hz (J_{F_a,F_e} 246, $J_{F_e,3}$ 6 Hz), F_a 3634 Hz ($J_{F_a,1}$ 6, $J_{F_a,3}$ 23 Hz); β-D anomer, F_e 4041 Hz (J_{F_a,F_e} 241, $J_{F_e,3}$ 6 Hz), F_a 2023 Hz ($J_{F_a,1}$ 17, $J_{F_a,3}$ 20.5 Hz). By contrast, the ^{19}F resonances[5] for 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-mannose were upfield with respect to C_6F_6.

As far as we are aware, "2,2-difluoroglucose" is the first example of a geminal difluoro sugar. Acetylated, 2,5-anhydro-1-deoxy-1,1-difluoro-D-mannitol is formed[8] on treatment of 3,4,6-tri-*O*-acetyl-D-glucal with lead tetraacetate–hydrogen fluoride.

The biological properties of the deoxyfluoro-D-hexose derivatives will be discussed in detail elsewhere, but it may be noted here that the 2-deoxy-2-fluoro derivatives of D-glucose and D-mannose, and the 2,2-difluoride **8**, strongly inhibit the growth in culture of lymphoma L5178Y cells, whereas 2-deoxy-2-chloro-D-glucose[5], 2-deoxy-2,2-dichloro-D-*arabino*-hexose[5], and the 3-, 4-, and 6-deoxy-6-fluoro derivatives of D-glucose have negligible inhibitory activity.

ACKNOWLEDGEMENT

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REFERENCES

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ANNOUNCEMENT

The first meeting of the French Carbohydrate Discussion Group will be held at Orsay (near Paris) from 12.00 on September 22nd to 12.00 on September 24th, 1971.

The theme of the Meeting will be "Carbohydrate Chemistry and Cancer Research", and four main topics will be included: I, Modified nucleosides and modified sugars; II, Glycoproteins in normal and neoplastic membranes; III, Carbohydrate derivatives in cancer chemotherapy; IV, Physicochemical and immunological methods in the estimation of carbohydrate transformations.

Accomodation will be in the University Halls of Residence, Faculty of Sciences, Orsay. Further information can be obtained from Professor L. Mester, Chairman of the French Carbohydrate Discussion Group, Institut des Substances Naturelles, C.N.R.S., 91-Gif-sur-Yvette, France.