Preliminary communication

4-Deoxy-4-fluoro-D-glucose

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In connection with a study of structure-activity relationships¹ involving substrates of hexokinase isozymes of normal and cancerous tissue², the complete series of deoxyfluoro-D-glucopyranose derivatives was required. The 2-, 3-, and 6-fluoro derivatives have been described³, and the α - and β -D-glucopyranosyl fluorides are known⁴. We now report on the sole remaining member of the series, 4-deoxy-4fluoro-D-glucose.

Treatment of 1,6-anhydro-4-O-toluene-p-sulphonyl- β -D-glucopyranose⁵ (1) with KHF₂ in boiling ethylene glycol for 75 min [monitoring by t.l.c., Kieselgel (Merck, 7731), ether-ethyl acetate (3:1)] gave 1,6-anhydro-4-deoxy-4-fluoro- β -D-glucopyranose (3, 47%; presumably *via* the epoxide **2**, *cf.* ref. 6), m.p. 118–120° (from acetone-ether), [α]_D -53° (*c* 2, water) (Found: C, 44.35; H, 5.45; F, 11.3. C₆H₉FO₄ calc.: C, 43.9; H, 5.5; F, 11.7%). The diacetate **4** (85%, using pyridine-acetic anhydride) was a liquid, b.p. 120–140° (bath)/0.15 mmHg, [α]_D - 49° (*c* 1.7, chloroform) (Found: C, 48.35; H, 5.25; F, 7.35. C₁₀H₁₃FO₆ calc.: C, 48.4; H, 5.25; F, 7.65%).



Hydrolysis of the fluoro-anhydride 3 with refluxing N hydrochloric acid for 16 h [t.l.c. monitoring, ether-ethyl acetate (5:1)], followed by neutralisation with silver carbonate, gave 4-deoxy-4-fluoro-D-glucose (5, 56%), m.p. 187-189° [from ethanol-light petroleum (b.p. 40-60°)], $[\alpha]_D + 26$ (9 min) $\rightarrow + 49^\circ$ (76 h, equil., c 1, water), R_G 2.53 on Whatman No. 1 paper with butyl alcohol-acetic acid-water (5:2:3) and detection with alkaline silver nitrate (Found: C, 39.85; H, 5.95; F, 10.3. C₆H₁₁FO₅ calc.: C, 39.55; H, 6.05; F, 10.45%). Treatment of the fluoro sugar 5

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with sodium acetate in boiling acetic anhydride for 20 min, followed by elution of the isolated product mixture from Kieselgel (Merck, 7734) with light petroleum (b.p. 40-60°)-ether (1:2), gave the β -D-tetra-acetate 6 (31%), m.p. 127-129° (from ethanol), $[\alpha]_D -32°$ (c 0.5, chloroform) (Found: C, 48.3; H, 5.65; F, 5.7. C₁₄H₁₉FO₉ calc.: C, 48.0; H, 5.4; F, 5.4%).

The structure of 4-deoxy-4-fluoro-D-glucose was unequivocally established on the basis of n.m.r. data for the β -D-tetra-acetate 6, for which the relevant coupling constants (Hz) were obtained from a spectrum, for a solution in deuteriochloroform, measured with a Varian HA-100 spectrometer operating in the frequency-sweep mode for ¹H resonances and (at 94 MHz) in the locked, field-sweep mode for¹⁹F resonances: $J_{1,2}$ 8.1, $J_{2,3}$ 9.5, $J_{3,4}$ 8.8, $J_{4,5}$ 10.0, $J_{5,6'}$ 2.5, $J_{5,6''}$ 4.4, $J_{6',6''}$ 12.4, $J_{F,3}$ 14.5, $J_{F,4}$ 49.5, $J_{F,5} \sim 2.6$, $J_{F,6'} \sim 1.6$, $J_{F,6''} \sim 1.5$. The magnitude of the vicinal H-H couplings are indicative⁷ of *trans* di-axial relationships and therefore of the gluco configuration. Also of importance are the relatively small magnitudes of $J_{F,3}$ and $J_{F,5}$ which are consistent with an *eq* fluorine atom flanked by *ax* protons.

A complete analysis of the n.m.r. spectrum of the fluoro-anhydride 4 was also possible. With the exception of the ¹⁹F-¹H couplings, the ¹H n.m.r. spectrum is remarkably similar to that of 2,3,4-tri-O-acetyl-1,6-anhydro- β -D-glucopyranose ⁸. Although, for compound 4, the vicinal F-H and H-H couplings do not permit unequivocal assignment of configuration at C-4, an assignment is possible on the basis of ⁴J values. The values $J_{F,6\,endo}$ 0.7 and $J_{F,6\,exo}$ 4.4 Hz accord with the known⁹ stereospecificity of ⁴J, ¹⁹F-¹H couplings, provided that the fluorine atom at C-4 is assigned to an axial position (7). This would give rise to a near-planar W arrangement of F-4 and *exo*-H-6, with the consequent, relatively large coupling as observed. The absence of a $J_{F,2}$ coupling in compound 4 is also consistent with an axial disposition of F-4.

A full analysis of the n.m.r. data will be presented elsewhere.

The low yield in the conversion of 1,6-anhydro-D-glucose into the 4-toluene-*p*-sulphonate largely deprives the above synthesis of convenience as a route for the large-scale preparation of 4-deoxy-4-fluoro-D-glucose, and alternative synthetic approaches are being investigated.

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