Note

Long-range (^5J) F–H coupling in carbohydrate derivatives containing the grouping C(OMe)–CF

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In a previous paper[1], a small, long-range coupling (0.8 Hz) was observed between the fluorine substituent and the protons of one of the methyl groups in methyl 6-*O*-acetyl-4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**1**); the alternative F–H couplings are ^5J for MeO-3 and ^6J for MeO-2. In order to gain more information on this type of long-range coupling, attention was turned initially to compounds in which ^5J F–H coupling only is possible between F–OMe. Two relevant series of compounds, each of which comprises a complete set of *ax* and *eq* variations of the substituents on C-1 and C-2, are (*1*) the methyl α- and β-glycopyranosides of 2-deoxy-2-fluoro-D-glucose and the *manno* analogue, and (*2*) the α- and β-glycopyranosyl fluorides of 2-*O*-methyl-D-glucose and the *manno* analogue. We now report briefly on the latter series.

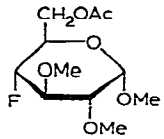
Conventional treatment[1,2] of the αβ-tetra-acetate of 2-*O*-methyl-D-glucose[3] (obtained by treatment of the free sugar with pyridine–acetic anhydride) with anhydrous hydrogen fluoride at −10° gave the thermodynamically more-stable α-D-glucosyl fluoride **2**. The β-D anomer **3** was obtained by treatment of the above αβ-tetra-acetate in sequence[1,2] with hydrogen bromide–acetic acid and silver monofluoride–acetonitrile.

Likewise, treatment of 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-β-D-mannopyranose[4] with anhydrous hydrogen fluoride gave the α-D-mannopyranosyl fluoride **4**. However, **4** also resulted when the reagent sequence hydrogen bromide–acetic acid and silver monofluoride–acetonitrile was applied to the tetra-acetate. It is possible that the intermediate α-D-mannopyranosyl bromide, in which the substituents at C-1 and C-2 are *trans*-diaxial, fails to yield the β-fluoride because of the participation of MeO-2 in the displacement reaction at C-1. This type of participation has been postulated for the reaction of *trans*-1-bromo-2-methoxycyclohexane with silver acetate which yields the *trans*-1-acetoxy derivative[5].

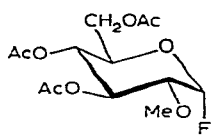
^5J F–H-coupling was observed between F-1 and MeO-2 in each of the glycosyl fluorides **2** (1.0 Hz), **3** (1.4 Hz), and **4** (0.55 Hz), where the orientation of the two

substituents is, respectively, *eq–ax*, *eq–eq*, and *ax–ax*. These data suggest that F–H coupling between vicinal fluorine and methoxyl substituents is likely to be a general phenomenon and therefore of value as a diagnostic in structural determination. However, since the variation in magnitude of the ^5J values is relatively small, a wider range of examples will be necessary before any firm conclusion can be drawn about the geometrical dependence of this long-range coupling.

The data presented herein support the conclusion[1] that it is the protons in MeO-3 which are coupled to F-4 in the glucoside **1**.



1



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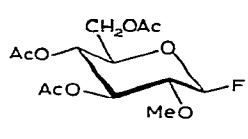

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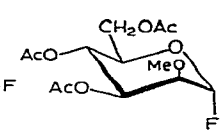

4

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were obtained for 0.5–2% solutions in chloroform (unless stated otherwise), using a Perkin–Elmer 141 polarimeter (path length, 1 dm). Thin-layer chromatography was performed on Kieselgel (Merck 7731) and detection was effected with conc. sulphuric acid.

N.m.r. spectra were obtained 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 94 MHz for ^{19}F resonances and at 100 MHz for ^1H resonances.

2-O-Methyl-D-glucose. — When prepared essentially by the method of Oldham and Rutherford[3], 2-*O*-methyl-D-glucose had m.p. 157–159° (from ethanol), $[\alpha]_D^{25}$ +66.5° (equil., *c* 1, water); lit.[3] m.p. 157–158°, $[\alpha]_D$ +65° (equil., water). Paper electrophoresis of 2-*O*-methyl-D-glucose in borate buffer[6] (pH 9.0) and detection with alkaline silver nitrate[7] gave one spot having M_{GLC} 0.3, but t.l.c. (ethyl acetate–ethanol, 9:1) showed two components (R_F 0.25, 0.27) in approximately equal proportions. When each component was extracted from a preparative-layer plate with methanol and then subjected to t.l.c., two-component mixtures identical with that originally observed were regenerated. The two components are probably anomers. 2,3,4,6-Tetra-*O*-methyl-D-glucopyranose gives two spots (R_F 0.1, 0.13) in t.l.c. (ethyl ether), as does 2,3,4,6-tetra-*O*-methyl-D-galactopyranose[8] on methyl sulphoxide-treated paper [ethyl ether–methyl sulphoxide (25:1); R_F 0.47, 0.52].

3,4,6-Tri-O-acetyl-2-O-methyl-α- and β-D-glucopyranosyl fluorides. — (*a*) A solution of syrupy 1,3,4,6-tetra-*O*-acetyl-2-*O*-methyl-αβ-D-glucopyranose (0.7 g, prepared by conventional treatment of the free sugar with pyridine–acetic anhydride) in liquid hydrogen fluoride (3 ml) was stored at −10° for 1 h, and then at room temperature for 1 h. The solution was poured into a well-stirred mixture of water (50 ml) and chloroform (50 ml), and neutralised with saturated, aqueous sodium hydrogen carbonate. The chloroform layer was washed twice with water, dried

($MgSO_4$), and concentrated in the presence of Kieselgel (~3 g). The residue was placed on a column of dry Kieselgel (~25 g) and eluted with benzene–ethyl ether (9:1) to give 3,4,6-tri-*O*-acetyl-2-*O*-methyl-α-D-glucopyranosyl fluoride (**2**, 350 mg, 56%), m.p. 74–76° (from ethanol–light petroleum), $[\alpha]_D^{26}$ +116° (Found: C, 48.6; H, 5.7; F, 6.0. $C_{13}H_{19}FO_8$ calc., C, 48.4; H, 5.9; F, 5.9%). N.m.r. data, $J_{1,2}$ 2.5 (*gauche* H–H), $J_{F,2}$ 24.4 (*trans*-diaxial F–H), $J_{F,Me}$ 1.0 Hz.

(*b*) The foregoing αβ-mixture of tetra-acetates (1 g) dissolved in a 40% solution of hydrogen bromide in glacial acetic acid was stirred at room temperature for 30 min, after which time t.l.c. (benzene–ethyl ether, 9:1) showed the absence of starting material. Evaporation was effected first at 40°/~15 mmHg and then at 50°/0.3 mmHg. Toluene (3 × 10 ml) was evaporated from the resulting syrup which was then dissolved in dry acetonitrile (5 ml) and stirred vigorously at room temperature for 1 h with silver monofluoride (1 g). The filtered mixture was then concentrated under diminished pressure, and the residue was partitioned between water (50 ml) and benzene (50 ml). The benzene layer was washed with water and concentrated. Recrystallization of the residue from ethanol–light petroleum gave 3,4,6-tri-*O*-acetyl-2-*O*-methyl-β-D-glucopyranosyl fluoride (**3**, 350 mg, 39%), m.p. 75.5–76.5°, $[\alpha]_D^{26}$ +58° (Found: C, 48.3; H, 5.9; F, 5.9%). N.m.r. data: $J_{1,2}$ 6.4 (*trans*-diaxial H–H), $J_{F,2}$ not resolvable, $J_{F,Me}$ 1.4 Hz.

3,4,6-Tri-O-acetyl-2-O-methyl-α-D-mannopyranosyl fluoride (**4**). — 1,3,4,6-Tetra-*O*-acetyl-2-*O*-methyl-β-D-mannopyranose[4] (900 mg) was treated with anhydrous hydrogen fluoride (1.5 ml) at −10° for 10 min, and then at room temperature for 20 min. The reaction mixture was worked up as described above for the *gluco* isomer, and the syrupy product (630 mg, 79%) was eluted from Kieselgel with ethyl ether–light petroleum (2:1). The α-fluoride had b.p. 150–60° (bath)/0.1 mmHg, $[\alpha]_D^{26}$ +26° (Found: C, 48.6; H, 6.2; F, 5.4%). N.m.r. data: $J_{1,2}$ +2.1 (*gauche* H–H), $J_{F,2}$ +0.8 (*gauche* F–H), $J_{F,Me}$ 0.55 Hz.

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REFERENCES

1 A. D. Barford, A. B. Foster, J. H. Westwood, L. D. Hall, and R. N. Johnson, *Carbohyd. Res.*, 19 (1971) 49.
2 F. Micheel and A. Klemer, *Advan. Carbohyd. Chem.*, 16 (1961) 85.
3 J. W. H. Oldham and G. J. Rutherford, *J. Amer. Chem. Soc.*, 54 (1932) 1086.
4 J. O. Deferrari, E. G. Gros, and I. O. Mastronardi, *Carbohyd. Res.*, 4 (1967) 432.
5 S. Winstein and R. B. Henderson, *J. Amer. Chem. Soc.*, 65 (1943) 2196.
6 A. B. Foster, *Advan. Carbohyd. Chem.*, 12 (1957) 81.
7 W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature (London)*, 166 (1950) 444.
8 B. Wickberg, *Methods Carbohyd. Chem.*, 1 (1962) 33.