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Syntheses of Some Furanosidic D-Fructose Derivatives

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The syntheses of α- and β-penta-*O*-acetyl-D-fructofuranose and of α- and β-1,3,4,6-tetra-*O*-acetyl-D-fructofuranosyl fluoride are reported. The substances were characterized by their ^{1}H and ^{13}C NMR spectra.

The chemistry of D-fructose and its derivatives has been summarized.[1,2] When glycosidically linked in natural products, D-fructose always occurs in the β-D-furanose form, therefore the synthesis of furanosidic D-fructose derivatives is of some interest. The recent finding that dextran may be synthesized by the action of dextransucrase on α-D-glucopyranosyl fluoride [3] raises the possibility of an analogous synthesis of levan from β-D-fructofuranosyl fluoride. We now report the synthesis of the latter substance, as the acetate, and of some other D-fructofuranose derivatives.

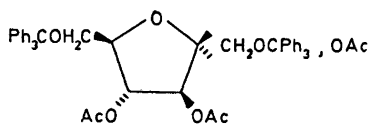
On acetolysis of 2,3,4-tri-*O*-acetyl-1,6-di-*O*-trityl-D-fructofuranose (*1*), Bredereck and coworkers [4] obtained a mixture of fully acetylated D-fructofuranoses. These have now been separated by chromatography on silica gel into the amorphous α-form (*2*, $[\alpha]_{578}^{22}$ +58°) and the β-form (*3*, m.p. 57–58 °C, $[\alpha]_{578}^{22}$ −9°). The starting material also is an anomeric mixture, as evident from its ^{13}C NMR spectrum (Table 1).

Treatment of the mixture of D-fructofuranose acetates with liquid hydrogen fluoride yielded the tetra-*O*-acetyl-α- and β-D-fructofuranosyl fluorides, which were fractionated by chromatography on silica gel. Neither of the products crystallized. The optical rotations were remarkably similar, $[\alpha]_{578}^{22}$ +45° for the α-form (*4*) and $[\alpha]_{578}^{22}$ +36° for the β-form (*5*), indicating different conformation for the two anomers.

The structures as well as the anomeric assignments of the penta-*O*-acetyl-D-fructofuranosyl fluorides follow from considerations of chemical shifts and coupling constants in the ^{1}H and ^{13}C NMR spectra (Table 1. For comparison, the chemical shifts of penta-*O*-acetyl-β-D-fructopyranose are also given). In agreement with previous findings,[5–8] the ^{13}C chemical shifts of the furanoses were 3–7 ppm higher than those for the same carbon atoms of the corresponding fructopyranoses. In their studies

Table 1. The ^{13}C NMR shifts in δ(ppm from TMS) of α- and β-D-fructofuranose pentaacetate (*2* and *3*); α- and β-D-fructofuranosyl fluoride tetraacetate (*4* and *5*); β-D-fructopyranose pentaacetate (*6*); the anomeric mixture of 1,6-dityityl-D-fructofuranose triacetate (*1*) and β-D-fructofuranose derivatives (Ref. 6).

	1	*2*	*3*	*4*	*5*	*6*	Ref. 6
C–2	109.4 105.4	107.9	104.9	117.5	113.9	102.3	~104.6
C–3	76.5–86.8	78.4	75.7	78.2	75.0	62.9–68.2	~77.6
C–4		80.6	79.5	83.5	80.2		~82.6
C–5		76.1	75.6	76.7	74.7		~75.1
C–1	62.3–64.6	61.8	63.7	61.2	61.7		~63.3
C–6		62.8	63.9	62.7	63.6		~62.6



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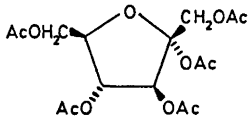

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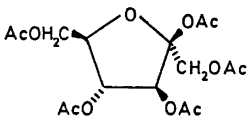

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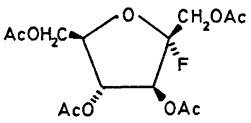

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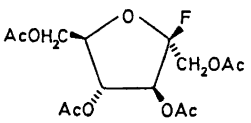

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of the ^{13}C NMR spectra of various furanosidic carbohydrates, Perlin and coworkers have shown that in hexulofuranoses with the *arabino*- and *ribo*-configurations (fructose and psicose), a *cis*-disposition of the hydroxyl group at C-3 and the methoxy group at C-2 gives rise to stronger shielding at C-2 than does the corresponding *trans*-disposition (methyl α-D-fructofuranoside 105.2 ppm and methyl β-D-fructofuranoside 102.4 ppm).[5] The anomeric C-2 therefore comes into resonance at lower field for the α-anomers than for the corresponding β-anomers. Application of this finding to the *2* and *3* furanosides gives the assignments shown (Table 1). Thus, the fructofuranose pentaacetate with δ 107.9 for the anomeric carbon atom is assigned the α-configuration (*2*), while that with the corresponding δ 104.9 is assigned the β-configuration (*3*). Similarly, in the tetra-*O*-acetyl-fructofuranosyl fluorides, the anomer with δ 117.5 for C-2 is assigned the α-configuration (*4*) and that with δ 113.9 for C-2 the β-configuration (*5*). The assignments for the pentaacetates are corroborated by the observed optical rotations. No such confirmation has been obtained for the tetra-*O*-acetyl-furanosyl fluorides (*4* and *5*). The reason for this is discussed below. However, these latter configurational assignments are confirmed by the observed ^{19}F-2, ^{1}H-3 coupling constants. Hall and coworkers [9] have reported $^{3}J_{H,F}$ 20.6 Hz for 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl fluoride (H-2 and F-1 *trans*-disposed), in agreement with the generally observed angular dependence of $^{3}J_{H,F}$ coupling constants.[10] We therefore assign the $^{3}J_{H,F}$ coupling constant of 7 Hz to tetra-*O*-acetyl-α-D-fructofuranosyl fluoride and that of about 16 Hz to the corresponding β-anomer.

The similarly of the optical rotations of the anomeric fructofuranosyl fluorides most probably reflects different conformational preferences. A preference for a quasi-axial orientation of the fluorine atom in each of the two anomers (anomeric effect) would lead to two different ring conformations. Conformations E_2 or $^{3}T_2$ [11] for the α-anomer appear compatible with the observed NMR coupling constants and ^{2}E or $^{2}T_0$ correspondingly for the β-anomer. (The indexes refer to the numbering in D-fructose.)

EXPERIMENTAL

General methods. Concentrations were performed under reduced pressure. Precoated plates with Silica Gel F_{254} (Merck) were used for TLC, and Silica Gel 60 (230–400 mesh, Merck) was used for column chromatography. Light petroleum refers to a fraction with b.p. 60–71 °C. NMR spectra were recorded with Varian A 60-A and Varian XL-100 instruments ($CDCl_3$ with TMS as internal reference). ^{1}H spectra were recorded at 60 and 100.1 MHz and ^{13}C spectra at 25.2 MHz. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

2,3,4-Tri-O-acetyl-1,6-di-O-trityl-D-fructo-furanose (1). 1,6-Di-*O*-trityl-D-fructose was prepared according to Bredereck *et al.*,[12] except that crystallization from pyridine was omitted. This product (16 g) was acetylated, worked up [12] and purified by chromatography on a silica gel column (80 × 8 cm), using light petroleum–ethyl acetate (3:1) as irrigant. The main product (8 g) was identified as a mixture of anomeric furanosides by ^{13}C NMR (Table 1).

Penta-O-acetyl-α- and β-D-fructofuranose (2 and 3). The trityl derivative *1* (5.8 g) was subjected to acetolysis and worked up as described by Bredereck.[4] TLC using light petroleum–ethyl acetate, 1:1, revealed two components in the derived syrup, the minor one having low mobility. The product was fractionated on a silica gel column (40 × 4 cm) using

light petroleum – ethyl acetate, 1:1, as irrigant. The minor component (0.3 g) was probably a tetraacetate as acetylation yielded a product with the same mobility as the pentaacetate. TLC demonstrated that the major component (2.4 g) was a mixture of two substances with slightly different mobilities. Separation of this material (1.4 g) on a silica gel column (30 × 3 cm), using the same irrigant, yielded the pure anomers, identified by their NMR spectra.

Penta-*O*-acetyl-α-D-fructofuranose (*2*, 1.05 g), $[\alpha]_{576}^{22}$ +58° (*c* 1.0, $CHCl_3$), was the faster component.

Penta-*O*-acetyl-β-D-fructofuranose (*3*, 330 mg), $[\alpha]_{578}^{22}$ −9° (*c* 1.0, $CHCl_3$). Crystals (ethanol), m.p. 57 – 58 °C. (Found: C 48.9; H 5.59. $C_{16}H_{22}O_{11}$ requires: C 49.2; H 5.68.)

*1,3,4,6-Tetra-*O*-acetyl-α- and β-D-fructofuranosyl fluoride (4 and 5).* The anomeric mixture of fructofuranose pentaacetates (*2* and *3*, 2.2 g) in liquid hydrogen fluoride (10 ml) was kept for 15 min at −15 °C and then for 15 min at 20 °C. The solution was poured into a stirred mixture of ice-water (100 ml) and chloroform (100 ml). The chloroform layer was separated and the aqueous phase extracted with chloroform (50 ml). The combined chloroform phases were washed with cold 1 M sodium hydrogen carbonate (2 × 50 ml), cold water (5 × 50 ml), dried ($MgSO_4$) and concentrated to a syrup. This was fractionated on a column of silica gel (40 × 4 cm) using light petroleum – ethyl acetate (1:1) as irrigant.

1,3,4,6-Tetra-*O*-acetyl-α-D-fructofuranosyl fluoride (*4*, 690 mg), $[\alpha]_{578}^{22}$ +45°, was eluted first.

1,3,4,6-Tetra-*O*-acetyl-β-D-fructofuranosyl fluoride (*5*, 430 mg), showed $[\alpha]_{578}^{22}$ +36°.

^1H NMR shifts and coupling constants. α-D-fructofuranose pentaacetate (*2*): δ 5.9 (H-3), 5.2 (H-4), 4.1 – 4.8 (H-1, H-5, H-6); $J_{3,4}$ 4 Hz, $J_{4,5}$ 6 Hz.

β-D-fructofuranose pentaacetate (*3*): δ ~5.7 (H-3, H-4), 4.5 – 4.7 (H-1, H-5, H-6); $J_{3,4}$ and $J_{4,5}$ probably small.

α-D-fructofuranosyl fluoride tetraacetate (*4*): δ 5.55 (H-3), 5.0 (H-4), 4.2 – 4.5 (H-1, H-5, H-6); $J_{F,3}$ 7; $J_{3,4}$ 1; $J_{4,5}$ 5.

β-D-fructofuranosyl fluoride tetraacetate (*5*): δ 5.4 – 5.7 (H-3, H-4), 4.2 – 4.5 (H-1, H-5, H-6); $J_{F,3}$ = 16; $J_{3,4}$ 7; $J_{4,5}$ small.

$^{13}C - ^{19}F$ coupling constants (Hz).

α-D-fructofuranosyl fluoride tetraacetate (*4*): $J_{F,1}$ 28.8; $J_{F,6}$ 0.5; $J_{F,3}$, $J_{F,4}$, $J_{F,5}$ 46.0, 1.5, 0.2; $J_{F,2}$ 226.8.

β-D-fructofuranosyl fluoride tetraacetate (*5*): $J_{F,1}$ 43.7; $J_{F,3}$, $J_{F,4}$, $J_{F,5}$ 20.9, 2.8, 0.4; $J_{F,2}$ 232.8.

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