SYNTHESES WITH ANHYDRO SUGARS. XII.*
PREPARATION OF 2,6-DIDEOXY-2-FLUORO-D-GLUCOSE**

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On reaction of 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose (*I*) with hydrogen bromide in acetic acid and in the presence of acetic anhydride 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranosyl bromide (*II*) was prepared, which was transformed by the action of sodium acetate to 1-O-acetyl derivative. Its dehalogenation on Raney nickel and deacetylation gave 2,6-dideoxy-2-fluoro-D-glucose (*X*). In a similar manner methyl 2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*IX*) and methyl 2-deoxy-2-fluoro-β-D-glucopyranoside (*XIV*) were prepared. Both substances are stable in acid medium and are not cleaved with emulsin.

In the literature much attention is devoted to the preparation of fluorinated hexose and pentose derivatives[1] which represent potential inhibitors of glycolysis. Fluorinated derivatives of deoxy sugars have been neglected so far, although, for example, dideoxy hexoses and their methyl ethers represent an important component of heart glycosides. In this paper we investigate the preparation of 2,6-dideoxy-2-fluoro-D-glucose in order to check the possibilities of the synthesis of this type of 6-deoxy-hexoses from relatively easily accessible fluoro derivatives of 1,6-anhydro-β-D-hexopyranoses. We were also interested in the change of the properties of the glycoside bond in the presence of fluorine in the molecule. As starting material we chose 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose[1] (*I*) but not 2-deoxy-2-fluoro-D-glucose[1,2], because the procedures for the preparation of 6-deoxy-D-glucose from D-glucose[3-6] described in the literature seemed less suitable in our case.

1,6-Anhydro derivative *I* was transformed to 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranosyl bromide (*II*) in 60% yield under the effect of hydrogen bromide in acetic acid and acetic anhydride. The by-product corresponding to 6-O-acetyl derivative *XII* was separated by crystallisation. The structure of dibromo derivative *II* was confirmed by PMR, optical rotation, and also by the course of subsequent reactions. On boiling with sodium acetate in acetic anhydride a highly

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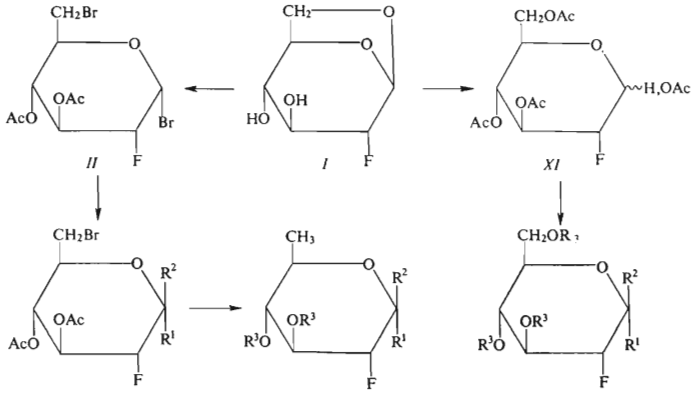
selective substitution of the relatively little reactive bromine on carbon $C_{(1)}$ took place under formation of a mixture of acetates *III* and *IV*, in which the β-anomer *IV* prevailed. Its optical rotation confirmed the configuration β and was in agreement with the J_{H_1,H_2} = 8 Hz. On reaction with sodium methoxide in methanol it gave the starting 1,6-anhydro derivative *I*. Reductive cleavage of bromine in the mixture of acetates



III, $R^1 = CH_3COO$, $R^2 = H$
IV, $R^1 = H$, $R^2 = CH_3COO$
V, $R^1 = H$, $R^2 = CH_3O$

XII, $R^1 = Br$, $R^2 = H$, $R^3 = CH_3CO$
XIII, $R^1 = H$, $R^2 = CH_3O$, $R^3 = CH_3CO$
XIV, $R^1, R^3 = H$, $R^2 = CH_3O$

VI, $R^1 = CH_3COO$, $R^2 = H$, $R^3 = CH_3CO$
VII, $R^1 = H$, $R^2 = CH_3COO$, $R^3 = CH_3CO$
VIII, $R^1 = H$, $R^2 = CH_3O$, $R^3 = CH_3CO$
IX, $R^1, R^3 = H$, $R^2 = CH_3O$
X, $R^1, R^3 = H$, $R^2 = HO$

Ac = acetyl

III and *IV*, using Raney nickel, gave a mixture of α and β-anomer of 6-deoxy derivatives *VI* and *VII* which could not be separated chromatographically, but by crystallisation. Catalytic deacetylation of both acetates, *VI* and *VII*, with sodium methoxide gave crystalline 2,6-dideoxy-2-fluoro-D-glucose (*X*) which is probably, according to its mutarotation, the β-anomer. Similarly as 2-deoxy-2-fluoro-D-glucose[1], it reduces Fehling's solution only weakly, even under heating.

Reaction of dibromo derivative *II* with methanol in the presence of silver oxide gave methyl 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*V*)

which was transformed on reductive dehalogenation to methyl 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*VIII*), and on subsequent deacetylation to the corresponding methylglucoside *IX*. Its structure was proved by optical rotation and oxidation with sodium periodate.*

Methyl 2-deoxy-2-fluoro-β-D-glucopyranoside (*XIV*), which we needed for the comparison with 6-deoxyglucoside (*IX*), was also prepared from 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose (*I*). The 1,6-anhydro link in compound *I* was acetolysed in acetic anhydride additioned with perchloric acid, and the mixture of anomeric acetates *XI* formed was transformed to 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (*XII*) on reaction with hydrogen bromide in acetic acid. From compound *XII* methyl 2-deoxy-2-fluoro-β-D-glucopyranoside (*XIV*) has been prepared by reaction with methanol and silver oxide and subsequent deacetylation. The value of optical rotation and the course of sodium periodate oxidation* correspond to the pyranoid structure *XIV* proposed.

The cleavage of the 1,6-anhydride bond in 1,6-anhydro derivatives of 2-deoxy-2-fluoro-D-glucose by hydrogen bromide in acetic acid (as described in this paper) takes place most probably by a primary cleavage of the $C_{(6)}$—$O_{(6)}$ bond, forming 6-bromo derivative, which reacts further, giving dibromo derivative *II*. Compounds *XI* and *XII* cannot be intermediates because under the same reaction conditions their acetoxy group is not substituted by bromine. Similarly, even after 20 hours reaction time 2,3,4-tri-O-acetyl-1,6-anhydro-β-D-glucopyranose gives rise practically only to 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, while 2,3,4-tri-O-acetyl-6-bromo-6-deoxy-α-D-glucopyranosyl bromide, which is the main product when liquid hydrogen bromide[8] was used, appears only in small amounts. In this case the cleavage of the $C_{(1)}$—$O_{(6)}$ bond takes place preferentially, according to our expectations.

The different type of cleavage of the 1,6-anhydro bond can be explained by the presence of the fluorine atom in the molecule, which by its −I effect stabilises the $C_{(1)}$—$O_{(6)}$ bond and thus enables the preferential cleavage of the $C_{(6)}$—$O_{(6)}$ bond. It can be expected that other atoms or groups with a similar electronegativity will also have a similar effect as fluorine atom. The fluorine atom also stabilises the glycoside bond, which is evident from the appreciable resistance of 2-fluoroglycosides *IX* and *XIV* toward acid hydrolysis in 0·5M-H_2SO_4 at 60°C, *i.e.* under the conditions for hydrolysing methyl β-D-glucopyranoside[9]. The hydrolysis of methyl 2-deoxy-2-chloro-β-D-glucopyranoside was studied from this point of view in detail by Buncel and Bradley[10]. Fluoroglycosides *IX* and *XIV* were also not cleaved in the presence of emulsin[11].

* Oxidation took place very slowly which might be caused by the presence of the fluorine atom in the molecule[7].

EXPERIMENTAL

Melting points were determined on a micro melting-point apparatus Boetius. Optical rotation was measured on an automatic polarimeter Bendix Ericsson UK Ltd., type 143 A, at 25°C. The PMR spectra were measured on a Tesla 80 MHz apparatus in deuteriochloroform with tetramethylsilane as internal standard (δ-scale). The course of some reactions was followed by thin-layer chromatography on silica gel according to Stahl in benzene–acetone 10 : 1 (detection with 50% sulfuric acid and carbonisation) and gas chromatography with a Chrom 3 apparatus, on a column 2·4 m long, 0·6 cm diameter, filled with Chromosorb W impregnated with 1.5% SE 30. The solutions were concentrated under reduced pressure at 40°C. The chloroform solutions were dried over anhydrous magnesium sulfate, unless stated otherwise. Samples for analysis were dried under reduced pressure over P_2O_5.

3,4-Di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranosyl Bromide (*II*)

A solution of 3·0 g of 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose[1] (*I*) in a mixture of 15 ml of acetic anhydride and 60 ml of anhydrous hydrogen bromide in acetic acid (39% solution) was allowed to stand at 20—25°C for 70 h and then heated at 70°C for 2·5 h in a sealed tube. After evaporation the residual syrup was dissolved in chloroform and washed with an aqueous solution of sodium hydrogen carbonate and water. The chloroform solution was dried, filtered, and evaporated and the residue (6·2 g) was crystallised from ethanol. The reaction course was observed by substracting small aliquots samples of the reaction mixture, which were analysed by thin-layer chromatography after working them up as above. Detection was carried out with sulfuric acid, or, specifically (for bromine), with a 5% benzenic solution of 4-(4′-nitrobenzyl)-pyridine, 5% NaOH, and heating. Compound *II* had R_F 0·64, the by-product *XII* R_F 0·55. Yield 4·0 g (60%), m.p. 139—140°C (sublimates about 124°C), $[\alpha]_D$ +209° (*c* 0·48; chloroform). PMR spectrum: 6·52 p.p.m. (H_1; J_{H_1,H_2} 4 Hz), 4·40 p.p.m. (CH_2Br, multiplet), 2·03 p.p.m. (2 CH_3COO). For $C_{10}H_{13}Br_2FO_5$ (392·0) calculated: 30·63% C, 3·34% H, 40·76% Br, 4·84% F; found: 30·86% C, 3·54% H, 39·79% Br, 4·70% F.

Mixture of 1,3,4-tri-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α- and β-D-Glucopyranose (*III* and *IV*)

A mixture of dibromo derivative *II* (1·0 g) and anhydrous sodium acetate (1·0 g) in 5 ml of acetic acid and 50 ml acetic anhydride was refluxed for 45 min. After cooling an aqueous solution of sodium hydrogen carbonate was added to the mixture which was evaporated to dryness. The residue was extracted with chloroform and the extract was washed with water, dried, and evaporated. The syrupy residue crystallised after addition of ethanol. Further crystallisation from ethanol gave 0·84 g (88%) of substances, m.p. 109—112°C (sinters at about 90°C), $[\alpha]_D$ +76° (*c* 0·5; chloroform). For $C_{12}H_{16}BrFO_7$ (371·2) calculated: 38·82 C, 4·34% H, 21·53% Br, 5·12% F; found: 38·88% C, 4·42% H, 21·21% Br, 5·21% F.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-fluoro-α- and β-D-Glucopyranose (*VI* and *VII*)

A solution of 2·0 g of a mixture of bromo derivatives *III* and *IV* in 25 ml of ethanol, 2·0 g of sodium hydrogen carbonate, 5 mg sodium iodide, and 10 ml of a Raney nickel suspension in ethanol[12] was shaken in a hydrogenation vessel with hydrogen. When the reaction ceased (after 2 h, controlled by gas chromatography) the mixture was filtered, ethanol distilled off, and the residue dissolved in chloroform. The chloroform layer was washed with water, dried, and evaporated to a syrup which was crystallised from a mixture of ether and light petroleum. Yield 1·42 g (84%), m.p. 80—110°C and 150—157°C. The product is a mixture of *VI* and *VII* in which *VI* prevails. By repeated crystallisation from a mixture of ether and light petroleum a relatively pure β-anomer *VII* was obtained, m.p. 153—157°C, $[\alpha]_D$ +69° (*c* 0·6; chloroform). PMR spectrum: 5·72 p.p.m. (H_1 quadruplet, J_{H_1,H_2} 8 Hz, $J_{H_1,F} \approx 4$ Hz), 2·11, 2·02, and 1·99 p.p.m. (3 CH_3COO), 1·17 p.p.m.

(C—CH_3 doublet, J_{H_5,H_6} 6 Hz). For $C_{12}H_{17}FO_7$ (292·5) calculated: 49·28% C, 5·86% H, 6·49% F; found: 49·40% C, 5·85% H, 6·45% F. From mother liquors after crystallisation of *VI* an insufficiently pure α-anomer was isolated, b.p. 80—90°C, $[\alpha]_D$ +172° (*c* 0·5); chloroform). PMR: 6·32 p.p.m. (H_1 doublet, $J_{H_1,H_2} \approx 4$ Hz), 2·14, 2·03, and 2·01 p.p.m. (3 CH_3COO), 1·13 p.p.m. (C—CH_3 doublet, J_{H_5,H_6} 6 Hz). For $C_{12}H_{17}FO_7$ (292·5) calculated: 49·28% C, 5·86% H, 6·49% F; found: 49·46% C, 5·87% H, 6·48% F.

2,6-Dideoxy-2-fluoro-D-glucose (*X*)

A mixture of 1·0 g of acetate *VI* and *VII* in 100 ml of absolute ethanol was deacetylated with sodium methoxide by standing at 20—25°C for 18 h. The solution was neutralised with Dowex 50 W cation exchanger and, after addition of a drop of acetic acid, it was evaporated to a syrup. After its dissolution in water and decolorization with charcoal the filtered solution was evaporated again and the residual syrup (0·35 g) was dissolved in ethyl acetate and then diluted with a small amount of light petroleum. After several days standing crystals separated which were filtered off under suction and washed with ethyl acetate. Yield 0·135 g (23%), m.p. 128—132°C, $[\alpha]_D$ +19° (after 2 min) → +39°, (after 50 min, equilibrium) (*c* 0·5; water). In butanol–toluene (9 : 1) saturated with water on a Whatman No 1 paper the R_F value of the substance was 0·43, R_X (X = thiourea) 1·00; detection with ammoniacal silver nitrate. In comparison with other reducing sugars the sensitivity of the detection was very low. For $C_6H_{11}FO_4$ (166·1) calculated: 43·37% C, 6·67% H, 11·43% F; found: 43·32% C, 6·68% H, 11·44% F.

Methyl 3,4-Di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*V*)

A mixture of 1·0 g of dibromo derivative *II*, 2·0 g of silver oxide, and 50 ml of methanol was stirred at 20°C. After about 30 min the reaction ceased and the solution was filtered. The filtrate was refiltered through a small layer of charcoal. The residue after the evaporation of methanol was crystallised from a mixture of ether–light petroleum. Yield 0·75 g (85·5%), m.p. 120—122°C, $[\alpha]_D$ +38° (*c* 0·6, chloroform). For $C_{11}H_{16}BrFO_6$ (343·2) calculated: 38·49% C, 4·70% H, 23·27% Br, 5·53% F; found: 38·53% C, 4·75% H, 23·04% Br, 5·57% F.

Methyl 3,4-Di-O-acetyl-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*VIII*)

A mixture of 1·0 g of bromo glycoside *V*, 1·0 g of sodium hydrogen carbonate, 5 mg of sodium iodide, 15 ml of Raney nickel suspension[12], and 30 ml of ethanol was shaken under hydrogen for 12 hours. The course of dehalogenation was followed by gas chromatography. The solution was filtered, ethanol distilled off, and the residue extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated to a syrupy residue which was crystallised from a mixture of ether and light petroleum. Yield 0·6 g (78%), m.p. 123—124°C, $[\alpha]_D$ +51° (*c* 0·6; chloroform). For $C_{11}H_{17}FO_6$ (264·3) calculated: 49·99% C, 6·49% H, 7·19% F; found: 50·19% C, 6·36% H, 7·20% F.

Methyl 2,6-Dideoxy-2-fluoro-β-D-glucopyranoside (*IX*)

Diacetate *VIII* (0·5 g) in 30 ml of methanol was deacetylated with sodium methoxide in the conventional manner. After 1 h reaction time the solution was neutralised with Amberlite IR 120, filtered through charcoal, and evaporated to dryness. The residual syrup (0·35 g) was crystallised from ether–light petroleum mixture. Yield 0·23 g (67%), m.p. 99—103°C, $[\alpha]_D$ −48° (*c* 0·66; water). On oxidation with sodium periodate[13] one equivalent of compound *IX* consumed 0·68

equivalents of periodate after 7 days standing at 25°C. For $C_7H_{13}FO_4$ (180·2) calculated: 46·66% C, 7·27% H, 10·54% F; found: 46·86% C, 7·32% H, 10·47% F.

Methyl 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside (*XIII*)

A solution of 1·0 g of 1,6-anhydro derivative *I* in 3·2 ml of freshly distilled acetic anhydride additioned with 0·03 ml of 70% perchloric acid (Merck) was allowed to stand at 20°C for 16 h. An aqueous solution of sodium hydrogen carbonate was added dropwise to the reaction mixture which was then extracted with chloroform. After drying the extract was concentrated to a syrup. The yield of the anomeric mixture of tetraacetates *XI* was 1·9 g (95%). Acetates *XI* (2 g) were dissolved in 5 ml of acetic anhydride and 20 ml of hydrogen bromide solution (39%) in acetic acid, and the mixture was allowed to stand at 20°C. The reaction course was followed chromatographically on a thin layer of silica gel. The substracted aliquots of the reaction mixture were worked up for analysis as described below. After the end of the reaction (approximately 2 h) the mixture was poured into water with ice, and the solution was extracted with chloroform. The extract was washed with sodium hydrogen carbonate, dried over anhydrous calcium chloride and filtered over a small column of charcoal. After evaporation of chloroform a syrupy bromoacetyl derivative *XII* was obtained in a 75% yield (1·6 g). A solution of *XII* (1·0 g) in 30 ml of methanol was shaken with 2·0 g of silver oxide at 20°C. After 30 min the reaction was over and the silver salts were filtered off and the solution was filtered through a column of charcoal. Methanol was distilled off and the residue crystallised from a mixture of ether and light petroleum. Yield of the glycoside *XIII* was 0·55 g (63%), m.p. 130–132°C, $[\alpha]_D$ +33° (*c* 0·58; chloroform). For $C_{13}H_{19}FO_8$ (322·3) calculated: 48·44% C, 5·94% H, 5·89% F; found: 48·75% C, 5·95% H, 5·97% F.

Methyl 2-Deoxy-2-fluoro-β-D-glucopyranoside (*XIV*)

Acetylated glycoside *XIII* (1·0 g) in 80 ml of methanol was deacetylated in the same manner as in the preparation of *IX*. The syrup obtained after evaporation of methanol was crystallised from a mixture of ethanol, ether, and light petroleum. Yield 0·35 g (57%), m.p. 148–150°C, $[\alpha]_D$ −29° (*c* 0·63; water). On oxidation with sodium periodate[13] 1·0 equivalent of glycoside *XIV* consumed after 7 days at 25°C 0·76 equivalents of the reagent. For $C_7H_{13}FO_5$ (196·2) calculated: 42·85% C, 6·67% H, 9·68% F; found: 42·84% C, 6·58% H, 9·81% F.

Attempt at Enzymatic Cleavage of Glycosides *IX* and *XIV* with Emulsin

To a solution of 5 mg of glycoside in 1·0 ml of water 1 mg of emulsin was added and the mixture was incubated at 40°C. Under the same conditions an experiment with methyl β-D-glucopyranoside was also carried out. The reaction course was followed by thin-layer chromatography. In the case of glycoside *IX* the chromatogram was run in methyl ethyl ketone–benzene–ethanol (15 : 15 : 1), in the case of glycoside *XIV* and methyl β-D-glucopyranoside in methyl ethyl ketone–methanol (15 : 1). After 50 h standing, when methyl β-D-glucopyranoside was practically completely cleaved to D-glucose, the solutions of glycosides *IX* and *XIV* remained unchanged.

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