SYNTHESES WITH ANHYDRO SUGARS. XI.*

PREPARATION OF 2-DEOXY-2-FLUORO-D-GLUCOSE AND 2,4-DIDEOXY-2,4-DIFLUORO-D-GLUCOSE**

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2-Deoxy-2-fluoro-D-glucose (*I*) and 2,4-dideoxy-2,4-difluoro-D-glucose (*II*) were synthetised by cleaving suitably substituted dianhydro derivatives prepared from 1,6:3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose (*III*), using KHF_2 in boiling ethylene glycol and subsequent hydrolysis of the 1,6-anhydro cycle by an aqueous solution of *p*-toluenesulfonic acid. 1,6-Anhydro-derivative of compound *II* may be obtained directly from compound *III* on reaction with KHF_2 in boiling ethylene glycol. The structures of both fluorinated deoxy derivatives of D-glucose were demonstrated by chemical reactions and by means of PMR spectra.

Fluorinated derivatives of deoxy monosaccharides belong to a field of sugar chemistry to which much attention has lately been devoted[1]. This follows mainly from the possibility of using these compounds as inhibitors of glycolysis or also as cytostatics[2–8]. The fluorinated derivative of D-ribose also forms a component of the antitrypanosomal antibiotic nucleocidine[9].

The commonest method of preparation of these compounds presently consists in the substitution of the sulfonyloxy groups of the saccharide derivatives, carried out with fluoride anion[10–20], or in the addition of fluoroxytrifluoromethane to the double bond of substituted glycals[21–23], or in the cleavage of the anhydro derivatives of sugars with hydrogen fluoride or potassium hydrogen fluoride[24–32].

In this paper the readily accessible 1,6 : 3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose[33,34] (*III*) was used as the starting material for the preparation of 2-deoxy-2-fluoro-D-glucose (*I*) and 2,4-dideoxy-2,4-difluoro-D-glucose (*II*). Compound *III* was transformed to 1,6-anhydro-4-O-benzyl-2-O-*p*-toluenesulfonyl-β-D-glucopyranose[33] (*IV*) in benzyl alcohol under the catalysis with *p*-toluenesulfonic acid, and *IV* on reaction with sodium methoxide gave 1,6 : 2,3-dianhydro-4-O-benzyl-β-D-mannopyranose[35] (*V*). On opening of its oxiran ring with potassium hydrogen fluoride in boiling ethylene glycol two isomeric fluorohydrins were formed in a 15 : 1 ratio which separated well on silica gel. The configuration D-*gluco VI* was assigned to the main product, and the configuration D-*altro VII* to its isomer. The preferential formation of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (*VI*),

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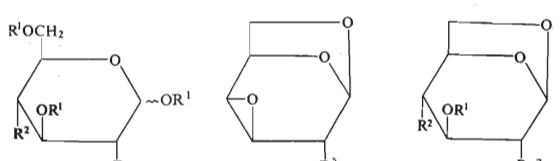
when compared with 1,6-anhydro-4-O-benzyl-3-deoxy-3-fluoro-β-D-altropyranose (*VII*), is in agreement with the Fürst-Plattner rule which is very useful in the determination of the configurations of compounds formed by the cleavage of epoxy derivatives of 1,6-anhydrohexoses; the main products of these cleavages are trans-diaxial derivatives[36].



I, $R^1 = H$, $R^2 = OH$
II, $R^1 = H$, $R^2 = F$
XI, $R^1 = Ac$, $R^2 = OAc$
XII, $R^1 = H$, $R^2 = OCH_2C_6H_5$
XVIII, $R^1 = Ac$, $R^2 = F$

III, R = OTs
XV, R = F

IV, $R^1 = H$, $R^2 = OCH_2C_6H_5$, $R^3 = OTs$
VI, $R^1 = H$, $R^2 = OCH_2C_6H_5$, $R^3 = F$
VIII, $R^1 = H$, $R^2 = OH$, $R^3 = F$
X, $R^1 = Ac$, $R^2 = OAc$, $R^3 = F$
XIV, $R^1 = H$, $R^2 = OTs$, $R^3 = F$
XVI, $R^1 = H$, $R^2 = R^3 = F$
XVII, $R^1 = Ac$, $R^2 = R^3 = F$
XXI, $R^1 = H$, $R^2 = F$, $R^3 = OTs$

Catalytic debenzylation of compounds *VI* and *VII* on palladium on charcoal gave 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose (*VIII*) and 1,6-anhydro-3-deoxy-3-fluoro-β-D-altropyranose (*IX*). The structure of *VIII* was proved by the reactions discussed below, including the formation of monotosylate *XIV* and epoxide *XV*, which show unambiguously the presence of a fluorine atom in the position 2; the D-*gluco* configuration is confirmed by the positive reaction of this compound with Bonner reagent[37] and the interpretation of the PMR spectrum of diacetate *X* and acetates of compounds *VI* and *VII* (Table I). From Table I it can be deduced that the mentioned compounds exist in chloroform solution in a chair conformation; this could be expected according to the analogy with acetylated derivatives of 1,6-anhydro-β-D-hexopyranoses[38,39]. The coupling constants are in good agreement with the literature data for hexopyranose fluoro derivatives[21,40–42].

The assignment of the structure to the acetates of compounds *VI* and *VII* was enabled mainly on the basis of the coupling constants of H_2, H_3 and H_3, H_4 which are approximately 9 Hz and 4·5 Hz for the acetyl derivative of compound *VII* (diaxial orientation of H_2, H_3, and axial-equatorial orientation of H_3, H_4), while in the case of the acetyl derivative of compound *VI* the *J*-constants are evidently lower because the mentioned atoms H_2, H_3, and H_4 are equatorial. Contrary to our expection it was not possible to make unambiguous conclusions on the structure from the couplings J_{H_1,F_2} and J_{H_1,F_3}. J_{H_1,F_2} is small (*anti*-periplanar arrangement of the $C_{(2)}$—$F_{(2)}$ and $C_{(1)}$—$O_{(6)}$[43] bonds), as follows from the band width for $H_1 \approx 6$ Hz, also comprising J_{H_2,H_1} and J_{H_3,H_1} which according to literature[39,44] are approximately 1·7 and 1·2 Hz. In comparison with this J_{F_3,H_1} is relatively large, *i.e.* 6·5 Hz (W system on a rigid skeleton).

When we compared the values of optical rotations of 1,6-anhydrohexopyranoses of D-*gluco* and D-*altro* configurations and of some of their derivatives, we found that the exchange of the hydroxy group for fluorine atom did not lead to a distinct change in optical rotation. This relationship will probably also be applicable to deoxyfluoro derivatives of other rigid systems (Table II). 2-Deoxy-2-fluoro-D-glucose (*I*) may

TABLE I

Characteristic PMR Parameters of Some Fluoro Derivatives of 1,6-Anhydro-β-D-hexopyranoses[a]

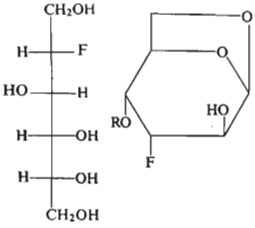
H_1	H_2	H_3	$H_4(H_5)$
	X		
5·57 um $w_{1/2}$ 6 Hz	4·24 d J_{H_2,F_2} 45 Hz $w_{1/2}$ 4 Hz	5·00 d J_{H_3,F_2} 17 Hz $w_{1/2}$ 5 Hz	4·64 cm (4·64 cm)
	Acetyl derivative[b] of compound *VI*		
5·57 um $w_{1/2}$ 6 Hz	4·25 d J_{H_2,F_2} 45 Hz $w_{1/2}$ 4 Hz	5·14 d J_{H_3,F_2} 17 Hz $w_{1/2}$ 5 Hz	3·25 um $w_{1/2}$ 4 Hz (4·60 cm)
	Acetyl derivative[b] of compound *VII*		
5·52 q J_{H_1,H_2} 1·5 Hz J_{H_1,F_3} 6,5 Hz	5·23 o J_{H_1,H_2} 1,5 Hz J_{H_2,H_3} 9 Hz J_{H_2,F_3} 13 Hz	4·78 o J_{H_2,H_3} 9 Hz J_{H_3,H_4} 4,5 Hz J_{H_3,F_3} 48 Hz	3·91 – 3·99 q (4·65 cm)
	XVII		
5·57 um $W_{1/2}$ 6 Hz	4·38 d J_{H_2,F_2} 45 Hz	5·125 tr[c] J_{H_3,F_2} } 17·5 Hz J_{H_3,F_4} }	≈4·23 d $J_{H_4,F_4} \approx 45$ Hz (4·78 cm)

[a]The spectra were measured on a Varian HA-100 apparatus in deuteriochloroform, tetramethylsilane as internal standard. Chemical shifts are given in p.p.m. in δ-scale; um = unresolved multiplet; d = doublet; cm = center of the multiplet; q = quadruplet; o = octet; $w_{1/2}$ = half width of the band. Methylene group CH_2 of the 1,6-anhydro bridge forms an ABX system with H_5 in the 3·70–4·00 δ region. The coupling constants were read from 250 sweep width chart, with a ±0·5 Hz error; first order analysis. [b]Acetyl derivatives of compounds *VI* and *VII* were prepared on acetylation with acetic anhydride in pyridine, by standing at room temperature for 24 hours. After pouring the mixture into water and extraction with chloroform the extract was washed with dilute hydrochloric acid, water, and then dried over anhydrous calcium chloride. It was evaporated *in vacuo* to dryness (syrup). The methylene groups of the benzyl ethers form an AB system: in the case of acetate *VI* the δ values of the centres of doublets were 4·67 and 4·85, $J_{A,B}$ = 12·5 Hz; for acetate *VII* δ 4·69 and 4·91, $J_{A,B}$ 12·5 Hz. [c]The triplet is composed of symmetrical quintuplets J_{H_3,H_1}; J_{H_3,H_2}; J_{H_3,H_4}; $J_{H_3,H_5} \approx 1{\cdot}5$ Hz.

be prepared by hydrolysis of compound *VIII* only under relatively drastic conditions, which is due evidently to the effect of the strongly electronegative fluorine atom on carbon $C_{(2)}$, because this atom decreases by its $-I$ effect the electron density of the oxygen atoms which are the components of both cycles. By this the ease of protonation of the oxygen atom of the 1,6-anhydro ring (which is the prerequisite of its successful cleavage) is decreased. This behaviour is in agreement with the stability of the 1,6-anhydro ring in compounds also containing at $C_{(2)}$ the strongly electro negative *p*-toluenesulfonyloxy group[45]. The hydrolysis of compound *VIII* could be carried out only at 165°C in a sealed tube under the effect of 1% aqueous solution of *p*-toluenesulfonic acid (3 hours). The hydrolysis did not take place on one hour reaction with 1% aqueous sulfuric acid in a sealed tube at 130°C or with 10% aqueous solution of this acid at boiling water bath temperature.

After the elimination of *p*-toluenesulfonic acid with Amberlite IR-45 2-deoxy-2-fluoro-D-glucose (*I*) was obtained in crystalline form, showing an appreciably decreased reducing ability toward Fehling's reagent in comparison with unsubstituted hexoses. By acetylation of *I* with acetic anhydride and sodium acetate a mixture of corresponding anomeric acetates *XI* is easily formed which after deacetylation affords 2-deoxy-2-fluoro-D-glucose (*I*). Reaction of *I* with phenylhydrazine did not give a chemically pure phenylhydrazone.

2-Deoxy-2-fluoro-D-glucose (*I*) was also formed instead of expected 4-O-benzyl-2-deoxy-2-fluoro-D-glucopyranose (*XII*) during the hydrolysis of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-D-glucopyranose (*VI*) with a 1% aqueous solution of *p*-toluenesulfonic acid at 165°C. Hence, the splitting of the 1,6-anhydro cycle is under the given conditions connected with the splitting off of the O-benzyl group. Reduction of 2-deoxy-2-fluoro-D-glucose (*I*) with sodium borohydride gave 2-deoxy-2-fluoro-D-glucitol (*XIII*). On partial tosylation of 1,6-anhydro-2-fluoro-β-D-glucopyranose (*VIII*) 1,6-anhydro-2-deoxy-2-fluoro-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XIV*) was obtained which on reaction with sodium methoxide in methanol gave 1,6 : 3,4-dianhydro-2-deoxy-2-fluoro-β-D-galactopyranose (*XV*). The formation of this compound, as well as its cleavage with benzyl alcohol, under catalysis with *p*-toluenesulfonic acid, to benzyl ether *VI* (the main product during the opening of the oxiran ring of dianhydro derivative *V*) shows again that the D-*gluco* configuration was justly assigned to the compound *VI*, that epoxide *XV* must have the D-*galacto* configuration, and finally, that monotosylate *XIV*, from which it was formed, contains the *p*-toluenesulfonyloxy group on carbon $C_{(4)}$. The structure of monotosylate *XIV* and also of epoxide *XV* is also supported by the values of their specific rotations (Table II). When boiled with potassium hydrogen fluoride in ethylene glycol compound *XV* is cleaved in its 3,4-anhydro ring under formation of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVI*). The second possible isomer, *XIX*, was not isolated from the reaction mixture. The structure of compound *XVI* is in agreement with the Fürst-Plattner rule and it also follows from the interpretation of the PMR spectra of its acetate *XVII* (Table I).



XIII *VII*, R = $C_6H_5CH_2$; *IX*, R = H *XIX*, R = H; *XX*, R = Ac *V*, R = $C_6H_5CH_2O$ *XXII*, R = F

TABLE II

Optical Rotation of Some 1,6-Anhydro-β-D-hexopyranoses and Their Fluoro Derivatives

Pyranose	$[\alpha_D]$	(solvent)
1,6-Anhydro-2-deoxy-2-fluoro-β-D-gluco- (*VIII*)	− 72°	(H_2O)
1,6-Anhydro-2,4-dideoxy-2,4-difluoro-β-D-gluco- (*XVI*)	− 62°	(H_2O)
1,6-Anhydro-β-D-gluco-[36]	− 66·5°	(H_2O)
1,6-Anhydro-β-D-gulo-[36]	+ 50·4°	(H_2O)
1,6-Anhydro-3-deoxy-3-fluoro-β-D-altro- (*IX*)	−194°	(H_2O)
1,6-Anhydro-β-D-altro-[36]	−213°	(H_2O)
1,6-Anhydro-2-deoxy-2-fluoro-4-O-p-toluenesulfonyl-β-D-gluco- (*XIV*)	− 58°	($CHCl_3$)
1,6-Anhydro-4-O-*p*-toluenesulfonyl-β-D-gluco-[46]	− 57°	($CHCl_3$)
1,6 : 3,4-Dianhydro-2-deoxy-2-fluoro-β-D-galacto- (*XV*)	− 63°	($CHCl_3$)
1,6 : 3,4-Dianhydro-β-D-galacto-[47]	− 84°	($CHCl_3$)

The parameters of acetate *XVII* are similar to the parameters of compound *X* and the acetate of compound *VI* and they confirm the structure of difluoro derivative *XVI*. An unambiguous decision between structure *XVII* and the second possible structure *XX* was possible on the basis of the chemical shift and the coupling constants of H_3 in acetate *XVII*, where H_3 forms a triplet with J_{H_3,F_4} and J_{H_3,F_2} 17·5 Hz. In the case of H_3 of the acetate of compound *XIX* a doublet of quadruplets with $J_{H_3,F_3} \sim 45$ Hz and $J_{H_4,H_3} \sim 8$ Hz and J_{H_3,F_2} 17—24 Hz would be more probable. Compound *XVI* belongs to the compounds with D-*gluco* configuration also by the value of its specific rotation, and not to compounds with D-*gulo* configuration (Table II).

Periodate oxidation[48] of 2,4-dideoxy-2,4-difluoro-D-glucose (*II*) is also in full agreement with the D-*gluco* configuration of compound *XVI*. In comparison with it, for the oxidation of the isomeric 2,3-dideoxy-2,3-difluoro-D-gulose a double amount of periodate would be necessary. The oxidation of compound *II* takes place much slower than that of compound *I*.

2,4-Dideoxy-2,4-difluoro-D-glucose (*II*) was prepared on hydrolysis of its 1,6-anhydro derivative *XVI* with 1% aqueous *p*-toluenesulfonic acid solution in a sealed tube at 175°C. In view of the presence of two fluorine atoms in the molecule the hydrolysis takes place still less rapidly than in the case of compound *VIII*; thus, even after 6 hours heating the starting material is still present in the reaction mixture. After the elimination of *p*-toluenesulfonic acid by Amberlite IR-45 a syrup was obtained which partly crystallised after several months standing. An attempt at the preparation of phenylhydrazone of *II* failed. On acetylation with acetic anhydride and sodium acetate it gave a syrupy triacetate, *XVIII*.

The reaction of 1,6 : 3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose (*III*) with potassium hydrogen fluoride in boiling ethylene glycol was carried out with the intention of preparing 1,6-anhydro-4-deoxy-4-fluoro-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XXI*) which is formed during the reaction of compound *III* with anhydrous hydrogen fluoride in dioxan[49]. Instead of the expected compound *XXI* another compound was isolated in 5% yield from the reaction mixture after extraction with ethyl acetate, representing the sole isolable sugar compound. Its IR spectra and melting point indicated that it is identical with 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVI*) which was prepared beforehand by the opening of epoxide *XV* with potassium hydrogen fluoride. The mechanism of formation of compound *XVI* from epoxide *III* can be represented by primary opening of the 3,4-anhydro ring with potassium hydrogen fluoride, giving 1,6-anhydro-4-deoxy-4-fluoro-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XXI*) as an intermediate, followed then by closing to 1,6 : 2,3-dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (*XXII*) under the basic effect of the fluoride anions. Compound *XXII* is then cleaved by excess potassium hydrogen fluoride to compound *XVI*.

Optimum reaction conditions found were heating of the mixture for 1·5 hours in boiling ethylene glycol. When the reaction time was prolonged a partial decomposition took place at the same temperature (epoxide *III* alone decomposed rapidly in boiling ethylene glycol), while at a temperature below 150°C the reaction almost did not take place. Low yields of compound *XVI* may be also explained by the assumption that in addition to the opening of the oxiran ring with the HF_2^- anion its cleavage with ethylene glycol also takes place under formation of 2-hydroxyethyl ether which cannot be extracted with ethyl acetate from aqueous ethylene glycol.

The direct transformation of compound *III* to compound *XVI* represents both a further confirmation of the correctness of our ideas on the configuration of the fluorinated saccharides described in this paper, and also – in spite of the low yields – a faster method of preparation of 2,4-dideoxy-2,4-difluoro-D-glucose (*II*) than is its synthesis *via* the epoxide *XV*, especially with respect to a relatively easy accessibility of the starting compound *III*.

The antibiotic activity of 2-deoxy-2-fluoro-D-glucose (*I*) and 2,4-dideoxy-2,4-difluoro-D-glucose (*II*), determined by the plate diffusion method using 4 bacterial strains (*Bacillus subtilis* UEM 8/58, *B. cereus* NRRL 569 B, *Escherichia coli* and *Mycobacterium phlei* PA) and 5 strains

of yeasts (*Candida albicans* 44, *Saccharomyces pastorianus*, *S. cerevisiae*, *Klöckera africana* ATCC 10.632, and *K. apiculata* NCIB 768), is negative.

EXPERIMENTAL

The melting points were measured on a Boetius micro melting point apparatus. Optical rotation was determined on a automatic polarimeter Bendix Ericsson UK Ltd, type 143 A, at 20°C. The course of reactions was followed by thin layer chromatography on silica gel G according to Stahl (layer strength 0·2—0·3 mm). Detection was carried out by mineralisation with 50% H_2SO_4 and heating. For column chromatography silica gel of 75—150 μ particle size was employed. Descending paper chromatography was carried out on a Whatman No 1 paper at 19—20°C in *n*-butanol–water. Detection was carried out with ammoniacal solution of silver oxide and heating, unless stated otherwise. The solvents were distilled off *in vacuo* at 20—50°C. Samples for analysis were dried over phosphorus pentoxide at 20—50°C (depending on the melting point of the sample) and 2 Torr.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (*VI*) and 1,6-Anhydro-4-O-benzyl-3-deoxy-3-fluoro-β-D-altropyranose (*VII*)

1,6:2,3-Dianhydro-4-O-benzyl-β-D-mannopyranose[35] (*V*) (3·6 g) was boiled with 8 g of potassium hydrogen fluoride in 120 ml of ethylene glycol for 1·5 h. During the reaction CO_2 was bubbled through the mixture. After cooling it was poured into 300 ml of a 5% aqueous solution of potassium carbonate and extracted 5 times with 50 ml of chloroform. After drying of the chloroform solution over anhydrous magnesium sulfate and evaporation of the solvent the obtained syrup (2·6 g) was chromatographed on a silica gel column (120 g). Elution with chloroform–acetone (9 : 1) gave two compounds the R_F values of which on thin layer were 0·60 and 0·52 (in the same system as used for elution). Both substances were crystallised from ether–light petroleum. Compound *VI*, having a higher R_F value, is the D-*gluco* isomer, m.p. 69°C, $[\alpha]_D$ −40° (1·12; chloroform), yield 1·55 g (40%). For $C_{13}H_{15}FO_4$ (254·3) calculated: 61·41% C, 5·95% H, 7·45% F; found: 61·47% C, 6·01% H, 7·31% F. Compound *VII* of the lower R_F value is the D-*altro* isomer, m.p. 102—103°C, $[\alpha]_D$ −95° (0·39, chloroform), yield approx. 100 mg (3%). For $C_{13}H_{15}FO_4$ (254·3) calculated: 61·41% C, 5·95% H, 7·45% F; found: 61·35% C, 5·94% H, 7·23% F.

1,6-Anhydro-2-deoxy-2-fluoro-β-D-glucopyranose (*VIII*)

Compound *VI* (1·0 g) in 20 ml of ethanol was hydrogenated on 0·5 g of 5% palladium on charcoal (Fluka) at normal pressure and at 40—50°C for 3·5 h. The catalyst was filtered off and the filtrate evaporated. The residue was crystallised from acetone–ether mixture. Yield 0·6 g (93%) of compound *VIII*, m.p. 129—130°C, $[\alpha]_D$ −72° (0·80, water). For $C_6H_9FO_4$ (164·1) calculated: 43·90% C, 5·53% H, 11·57% F; found: 43·78% C, 5·40% H, 11·53% F.

3,4-Di-O-acetyl-1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose (*X*)

Compound *VIII* (100 mg) was refluxed in 2 ml of acetic anhydride additioned with 100 mg of anhydrous sodium acetate for 1 h. Excess acetic anhydride was distilled *in vacuo* and the residue diluted with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and dried over anhydrous magnesium sulfate. After filtering and evaporation of ether the residual syrup crystallised out after 14 days standing. After recrystallisation from a mixture of ether and light petroleum approximately 100 mg (65%) of compound *X* were obtained, m.p. 60—61°, $[\alpha]_D$ −67·5° (1·00, chloroform). For $C_{10}H_{13}FO_6$ (248·1) calculated: 48·30% C, 5·25% H, 7·66 F; found: 48·52% C, 5·42% H, 7·46% F.

1,6-Anhydro-3-deoxy-3-fluoro-β-D-altropyranose (*IX*)

Compound *VII* (270 mg) was hydrogenated in 15 ml of ethanol under catalysis of 170 mg of 10% Pd on charcoal (Fluka) at normal pressure and 40—50°C for 80 min. After filtration the solvent was evaporated and the residual syrup crystallised out after addition of a few drops of ether. After recrystallisation from a mixture of acetone and ether compound *IX* was obtained in pure state, yield 135 mg (77%), m.p. 132—134°C, $[\alpha]_D$ −194° (0·18, water). For $C_6H_9FO_4$ (164·1) calculated: 43·90% C, 5·53% H, 11·57% F; found: 44·11% C, 5·46% H, 11·53% F.

2-Deoxy-2-fluoro-D-glucose (*I*)

a) 500 mg of compound *VIII* were heated with 45 ml of a 1% aqueous *p*-toluenesulfonic acid solution in a sealed tube at 165°C for 5 hours. The solution was filtered through a column of Amberlite IR-45 (diameter 1 cm, length 12 cm) which was then washed with 50 ml of water. From the eluate water was distilled off and the residual syrup was mixed with a small amount of methanol and heated. After standing in a refrigerator approximately 250 mg (46%) of crystals separated out. After recrystallisation from methanol the compound had m.p. 170—176°C, $[\alpha]_D$ +37° (2 min) → +62° (120 min) (0·80; water). R_F value in paper chromatography was 0·25, relative *R* value when 2-deoxy-D-glucose was taken as standard, was 1·1; detection with a 3% n-butanolic *p*-anisidine hydrochloride solution. It may also be detected with ammoniacal Ag^+ solution or with Bonner reagent. For $C_6H_{11}FO_5$ (182·1) calculated: 39·60% C, 6·05% H, 10·40% F; found: 39·49% C, 6·17% H, 10·19% F. On oxidation with periodic acid[50] 3 mol of reagent were consumed per 1 mol of this compound after 48 h, the reaction was carried out in a buffered solution of pH 6·8. *b*) A suspension of 1·55 g of benzyl ether *VI* in 40 ml of 1% aqueous *p*-toluenesulfonic acid solution was heated in a sealed tube at 165°C for 3 h. The reaction mixture was filtered through a column of Amberlite IR-45 (diameter 1 cm, length 25 cm) which was washed with 70 ml of water. The eluate was evaporated and the residual syrup crystallised after heating it with a small amount of ethanol. Crystallisation from ethanol and ether gave 0·9 g (80%) of compound, m.p. 177—179°C, $[\alpha]_D$ +38° (2 min) (0·66; water). The IR spectrum of this sample was identical with the IR spectrum of a sample prepared as under *a*).

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-D-glucopyranose (*XI*)

150 mg of compound *I*, 300 mg of anhydrous sodium acetate, and 3 ml of acetic anhydride were heated on a water bath for one hour. The mixture was poured into 20 ml of water and then extracted with three 30 ml portions of ether. After shaking of the ethereal extract with aqueous sodium hydrogen carbonate and drying over anhydrous magnesium sulfate, ether was evaporated. The syrupy residue crystallised after addition of a small amount of ether and light petroleum. After recrystallisation from a mixture of these solvents the m.p. was 78—92°C (representing evidently a mixture of α and β anomers). Yield 220 mg (76%), $[\alpha]_D$ +40° (0·70; chloroform). For $C_{14}H_{19}FO_9$ (350·3) calculated: 48·00% C, 5·47% H, 5·43% F; found: 48·32% C, 5·73% H, 5·40% F. On deacetylation of this acetate with sodium methoxide in methanol 2-deoxy-2-fluoro-D-glucose (*I*) was obtained in 80% yield, m.p. 172—175°C.

2-Deoxy-2-fluoro-D-glucitol (*XIII*)

To a mixture of 1,3 g of compound *I* in 15 ml of water a solution of 1 g of sodium borohydride in 25 ml of water was added under stirring, keeping the temperature below 50°C. The addition was finished after approximately 10 min. Amberlite IR-120 (H^+) was then added until the liberation of gas ceased, the solution was diluted to a 150 ml volume and the stirring was continued for another 10 min with additional 10 g of the same ion exchanger. After filtration the neutral

solution was evaporated. The residual syrup was dissolved in 40 ml of methanol and the solvent was evaporated. The residue crystallised out after several minutes standing. Recrystallisation from methanol gave compound *XIII*, m.p. 139–141°C, $[\alpha]_D$ −7° (0·66; water) in a 80% yield (1·05 g). For $C_6H_{13}FO_5$ (184·1) calculated: 39·13% C, 7·12% H, 10·33% F; found: 39·11% C, 7·15% H, 10·11% F.

1,6-Anhydro-2-deoxy-2-fluoro-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XIV*)

1·3 g of compound *VIII* in 5 ml of pyridine was mixed under stirring and cooling with a solution of 1·5 g of *p*-toluenesulfonyl chloride in 3 ml of pyridine and the mixture was allowed to stand at 5°C for 100 h. It was then poured into 100 ml of water and extracted with ether. The extract was washed with 5% hydrochloric acid, then with water and dried over anhydrous magnesium sulfate. After filtration and evaporation of ether a syrup was obtained which crystallised rapidly. On crystallisation from a mixture of benzene and light petroleum 0·76 (30%) of compound *XIV* were obtained, m.p. 101–103°C, $[\alpha]_D$ −58° (1·0; chloroform). For $C_{13}H_{15}FO_6S$ (318·3) calculated: 49·10% C, 4·75% H, 10·10% S, 5·97% F; found: 49·18% C, 4·77% H, 10·36% S, 5·89% F.

1,6:3,4-Dianhydro-2-deoxy-2-fluoro-β-D-galactopyranose (*XV*)

To a solution of 1·0 g of compound *XIV* in 10 ml of chloroform a solution of 0·5 g of sodium dissolved in 10 ml of methanol was added under cooling and stirring and the mixture was allowed to stand at 20°C for 1 h. It was then poured into 50 ml of water and the chloroform layer was separated. The aqueous layer was extracted with chloroform and the combined extracts were dried over anhydrous magnesium sulfate and filtered. Chloroform was evaporated and the residual syrup crystallised out. Pure compound *XV* was prepared by chromatography on a silica gel column with benzene–acetone (9 : 1); yield 0·4 g (90%), needles, m.p. 26–28°C $[\alpha]_D$ −63° (0·80; chloroform). For $C_6H_7FO_3$ (146·1) calculated: 49·32% C, 4·83% H, 13·00% F; found: 49·30% C, 4·89% H, 12·92% F.

Cleavage with benzyl alcohol: a mixture of 0·3 g of compound *XV*, 3 ml of benzyl alcohol, 2 ml of benzene, and 0·02 g of *p*-toluenesulfonic acid was heated in a sealed tube at 110°C for 8 hours. The mixture was poured into 10 ml of water, extracted with chloroform and the solvent evaporated. The residue was steam-distilled and then crystallised from a mixture of ether and light petroleum. Yield 0·1 g (20%) of crystals the m.p. and the IR spectrum of which were identical with those of compound *VI* obtained on cleavage of the epoxide ring of compound *V* with potassium hydrogen fluoride in ethylene glycol.

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVI*)

a) A mixture of 0·7 g of compound *XV*, 3·4 g of potassium hydrogen fluoride, and 60 ml of ethylene glycol was refluxed for 2 h while introducing into the mixture CO_2. Ethylene glycol was evaporated *in vacuo* and the residue extracted with ethyl acetate. The syrup obtained after the evaporation of solvent was purified by chromatography on a silica gel column with benzene–acetone (9 : 1); yield 0·16 g (20%), needles, m.p. 99–100°C, $[\alpha]_D$ −62° (0·82; water). For $C_6H_8F_2O_3$ (166·1) calculated: 43·38% C, 4·85% H, 22·88% F; found: 43·36% C, 4·73% H, 22·69% F. *b*) 20 g of compound *III* and 40 g of potassium hydrogen fluoride were refluxed with 400 ml of ethylene glycol for 100 min under CO_2 (slow bubbling). After cooling, the reaction mixture was poured into 1000 ml of water and extracted with three 300 ml portions of ethyl acetate. The extracts were combined, washed with saturated sodium hydrogen carbonate solution, and dried over anhydrous magnesium sulfate. After filtration with active charcoal the solvent was evaporated.

The remaining syrup (1·0 g) crystallised out and was recrystallised from chloroform. Yield 0·5 g (5%), m.p. 99—102°C. The IR spectrum of the material was identical with that of the crystals obtained as under *a*).

3-O-Acetyl-1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVII*)

A mixture of 0·2 g of compound *XVI*, 0·4 g of anhydrous sodium acetate, and 10 ml of acetic anhydride was refluxed for 15 minutes. After pouring it into water the mixture was extracted with chloroform and the extract washed with sodium carbonate solution and water, and then dried over anhydrous magnesium sulfate and concentrated. The remaining syrup crystallised out after several days standing. After crystallisation from benzene and light petroleum 0·1 g (46%) of compound *XVII* was obtained, m.p. 49—50°C, $[\alpha]_D$ −74° (0·84; chloroform). For $C_8H_{10}FO_4$ (208·2) calculated: 46·16% C, 4·84% H, 18·25% F; found: 46·41% C, 4·60% H, 18·16% F.

2,4-Dideoxy-2,4-difluoro-D-glucose (*II*)

A solution of 0·4 g of compound *XVI* in 20 ml of 1% aqueous *p*-toluenesulfonic acid solution was heated in a sealed tube at 175°C for 6 hours, the mixture was filtered through 4 g of Amberlite IR-45, and the filtrate was extracted with ethyl acetate. From this extract 0·1 g of the unreacted starting compound *XVI* was regenerated. The evaporation of the aqueous residue gave 0·2 g (50%) of a syrup which after several months standing partly crystallised m.p. 58—64°C. $[\alpha]_D$ +51° (0·83; water). In paper chromatography the product gave a single spot of R_F 0·46. It does not react with Bonner's reagent, and it reacts with ammoniacal Ag^+ solution and Fehling's reagent still less readily than compound *I*. On oxidation with sodium periodate according to Aspinall and Ferrier[48] it consumed 0·95 equivalents of the reagent per 1 equivalent of compound *II* after 240 h. It did not change further. For $C_6H_{10}F_2O_4$ (184·1) calculated: 39·13% C, 5·47% H, 20·64% F; found: 38·93% C, 5·85% H, 20·85% F.

1,3,6-Tri-O-acetyl-2,4-dideoxy-2,4-difluoro-D-glucose (*XVIII*)

A mixture of 0·2 g of compound *II*, 0·4 g of anhydrous sodium acetate, and 10 ml of acetic anhydride was refluxed for 20 minutes. After isolation carried out in the conventional manner 0·15 g (44%) of a syrup was obtained which would not crystallize; $[\alpha]_D$ +37° (0·87; chloroform). For $C_{12}H_{16}F_2O_7$ (310·3) calculated: 46·45% C, 5·20% H, 12·25% F; found: 46·51% C, 5·20% H, 12·09% F.

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