SYNTHESIS OF 1,6-DIDEOXY-1,6-DIFLUORO-D-FRUCTOSE*

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The reaction of 2,3-O-isopropylidene-1,6-di-O-p-toluenesulfonyl-β-D-fructofuranose (*I*) with potassium fluoride in boiling ethylene glycol afforded 1,6-dideoxy-1,6-difluoro-2,3-O-isopropylidene-β-D-fructofuranose (*IV*) which on acid hydrolysis gave 1,6-dideoxy-1,6-difluoro-D-fructose (*III*). Partial substitution of the *p*-toluenesulfonyloxy groups in compound *I* by a fluorine atom was not possible to effect. Unsuccessful was also the attempted preparation of 1-deoxy-1-fluoro-D-fructose from 2,3 : 4,5-di-O-isopropylidene-1-O-methanesulfonyl-β-D-fructopyranose (*XI*), 2,3 : 4,5-di-O-isopropylidene-1-O-*p*-nitrobenzenesulfonyl-β-D-fructopyranose (*XII*), and phenyl 3,4,5-tri-O-acetyl-1-O-methanesulfonyl-β-D-fructopyranoside (*XIII*). 2,3 : 4,6-Di-O-isopropylidene-1-O-*p*-toluenesulfonyl-α-L-sorbofuranose (*XV*) treated with potassium fluoride in boiling ethylene glycol splits off the isopropylidene group in 4,6 position.

The fluorinated deoxysaccharides have become in the last years a subject of interest[1]. Since almost all so far published syntheses of these compounds refer to aldoses, *e.g.*[2-10], we attempted the preparation of fluorinated derivatives of the ketoses D-fructose and L-sorbose.

From the literature[11,12] it is known that the sulfonyloxy groups in 2,3-O-isopropylidene-1,6-di-O-p-toluenesulfonyl-β-D-fructofuranose (*I*) are much more reactive than in 2,3 : 4,5-di-O-isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructopyranose (*II*). For this reason we tried in the first place the preparation of 1,6-dideoxy-1,6-difluoro-D-fructose (*III*) by heating compound *I*, prepared by a modification of method[12], with potassium fluoride in boiling ethylene glycol, and obtained 1,6-dideoxy-1,6-difluoro-2,3-O-isopropylidene-β-D-fructofuranose (*IV*). Replacement of ethylene glycol by dimethylformamide or liquid ammonia[13] has not proved successful. The NMR spectrum of compound *IV* confirms the presence of fluorine atoms in position 1 and 6. Compound *IV* is very stable and does not undergo any change on boiling for 10 h with 5% sodium hydroxide. Acid hydrolysis yields 1,6-dideoxy-1,6-difluoro-D-fructose (*III*).

* Partial results are contained in the Diploma Theses of V. Štěpán (Charles University, Prague 1961) and J. Halásková-Glogarová (Charles University, Prague 1964).

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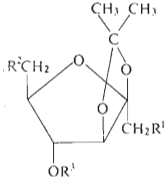
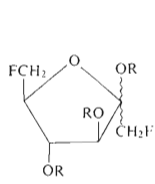
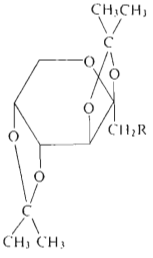
From compounds *III* and *IV* the crystalline acetates *V* and *VI* were prepared. Heating of 4-O-acetyl-2,3-O-isopropylidene-1,6-di-O-*p*-toluenesulfonyl-β-D-fructofuranose (*VII*) with potassium fluoride in ethylene glycol did not lead to compound *VI*, but deacetylation took place under formation of compound *IV*.

Of the two *p*-toluenesulfonyloxy groups in compound *I* is the group attached to $C_{(6)}$ more reactive towards nucleophilic reagents[14]. But this we were not able to prove when using the fluoride anion in ethylene glycol as the nucleophilic reagent,



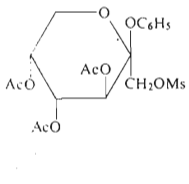




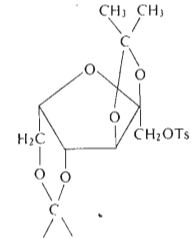
I; $R^1 = R^2 = OTs$, $R^3 = H$
IV; $R^1 = R^2 = F$, $R^3 = H$
VI; $R^1 = R^2 = F$, $R^3 = Ac$
VII; $R^1 = R^2 = OTs$, $R^3 = Ac$
VIII; $R^1 = OTs$, $R^2 = OAc$, $R^3 = Ac$
IX; $R^1 = OTs$, $R^2 = OH$, $R^3 = H$
X; $R^1 = OTs$, $R^2 = Bzo$, $R^3 = H$

III; R = H
V; R = Ac

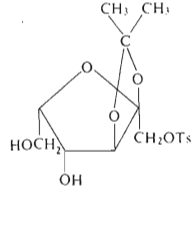
II; R = OTs
XI; R = OMs
XII; R = ONs
XIV; R = OH



XIII



XV



XVI

Ac = acetyl Bzo = benzoyloxy Ms = methanesulfonyl
Ts = *p*-toluenesulfonyl Ns = *p*-nitrobenzenesulfonyl

since there did not even at temperatures below the boiling point of the solvent take place partial exchange of the *p*-toluenesulfonyloxy group on $C_{(6)}$ under formation of the 6-deoxy-6-fluoroderivative of D-fructose. However, the exchange of this group was very easily effected by treatment with potassium acetate, to give 4,6-di-O-acetyl-2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructofuranose (*VIII*) as the reaction product, the deacetylation of which afforded 2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructofuranose (*IX*). The compounds *VIII* and *IX* do not give derivatives of 1-deoxy-1-fluoro-D-fructose when heated with potassium fluoride in ethylene glycol. In the same way behaves also 6-O-benzoyl-2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructofuranose (*X*), obtained from compound *I* by treatment with sodium benzoate in dimethylformamide.

We attempted also the preparation of 1-deoxy-1-fluoro-D-fructose by exchange of the methanesulfonyloxy, respectively *p*-nitrobenzenesulfonyloxy group by a fluorine atom in the compounds 2,3 : 4,5-di-O-isopropylidene-1-O-methanesulfonyl-β-D-fructopyranose[15] (*XI*), 2,3 : 4,5-di-O-isopropylidene-1-O-*p*-nitrobenzenesulfonyl-β-D-fructopyranose (*XII*), which compound we prepared from 2,3 : 4,5-di-O-isopropylidene-D-fructopyranose[16] (*XIV*), and phenyl 3,4,5-tri-O-acetyl-1-O-methanesulfonyl-β-D-fructopyranoside[15] (*XIII*) by using potassium or sodium fluoride in ethylene glycol, dimethylformamide or formamide at elevated temperatures. However, according to the reaction conditions, the compounds did either not react (*e.g.* compound *XI* can be recovered after boiling with NaF in dimethylformamide for ten hours), or gave a mixture of substances not containing fluorine. After heating compound *XI* with anhydrous KF in ethylene glycol under reflux for 90 minutes substance *XIV* was isolated. This substance was also present in the reaction mixture obtained by heating compound *XII* with potassium fluoride in dimethylformamide and formamide for 8 h at 160°C. Attempts to prepare the 1-deoxy-1-fluoro-L-sorbose derivative by refluxing 2,3 : 4,6-di-O-isopropylidene-1-O-*p*-toluenesulfonyl-α-L-sorbofuranose (*XV*) with potassium fluoride in ethylene glycol resulted in splitting off the O-isopropylidene group in 4,6 position under formation of 2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-α-L-sorbofuranose (*XVI*).

EXPERIMENTAL

Melting points were determined by a Boetius micro melting point apparatus. Optical rotations were measured on an automatic polarimeter Bendix-Ericsson UK Ltd., type 143 A, at 20°C. Thin layer chromatography was run on silica gel G according to Stahl (layer thickness 0·2—0·3 mm). Column chromatography was performed on silica gel of grain size 75—150 μ. The potassium fluoride used was the dihydrate and the solvents were anhydrous; drying was carried out with anhydrous magnesium sulfate unless otherwise stated.

2,3-O-Isopropylidene-1,6-di-O-*p*-toluenesulfonyl-β-D-fructofuranose (*I*)

To a solution of 2 lits of acetone, previously at 0°C dropwise treated with 75 ml concentrated sulfuric acid, were added 200 g of 1,6-di-O-*p*-toluenesulfonyl-D-fructofuranose[12] in 1 l of acetone. The solution was left for three hours at room temperature, then poured into 2 l of a saturated aqueous solution of potassium carbonate cooled to 0°C. The deposited salts were filtered off and the formed layers separated. The lower aqueous layer was extracted with 500 ml of chloroform, and the combined organic phases were dried and then evaporated. The residue was recrystallized from methanol or from acetone–methanol mixture; yield 60 g (about 20% referred to D-fructose), m.p. 134—135°C, in agreement with the literature[12]. From the mother liquors may be precipitated with water a further part of the product.

1,6-Dideoxy-1,6-difluoro-2,3-O-isopropylidene-β-D-fructofuranose (*IV*)

10 g of compound *I* were refluxed with a solution of 10 g potassium fluoride in 100 ml of ethylene glycol for 4 h, and simultaneously was bubbled through carbon dioxide. After diluting with 500 ml of water was the mixture for 6 h continuously extracted with ethyl acetate. The extract was shaken with a small amount of water and the aqueous layer then shaken again with the same volume of ethyl acetate. The combined ethyl acetate extracts were dried and then evaporated *in vacuo*. The syrupy residue was chromatographed on silica gel (65 g) in the solvent system benzene–acetone (19 : 1), yield 1·7 g, m.p. 56–59°C, yield after recrystallization from light petroleum 1·4 g (40%) of compound *IV*, m.p. 60–62°C, $[\alpha]_D$ +8° (*c* 2·0; chloroform). Chromatographed on a thin layer of silica gel (with gypsum) in the solvent system benzene–acetone (9 : 1) it had an R_F value of 0·70, whereas the starting compound had under the same conditions an R_F of 0·75. When using the system according to Codington and coworkers[17], the compound *IV* has, however, a higher R_F value (0·36) than compound *I* (R_F 0·20). For $C_9H_{14}F_2O_4$ (224·2) calculated: 48·14% C, 6·30% H, 16·98% F; found: 48·42% C, 6·36% H, 16·99% F. PMR spectrum (deuteriochloroform; p.p.m., δ scale): 1·35 and 1·54 (2 CH_3, singlet), 2·88 (—OH, broad band), 4·52 ($C_{(1)}H_2F$ doublet, $J_{H,F}$ = 47 Hz), 4·57 ($C_{(6)}H_2F$ doublet of doublets, $J_{H,F}$ = 47 Hz, $J_{H_{6,6'}H_5}$ = 5 Hz). The protons H_3, H_4, and H_5 were not assigned.

4-O-Acetyl-1,6-dideoxy-1,6-difluoro-2,3-O-isopropylidene-β-D-fructofuranose (*VI*)

220 mg of compound *IV* were dissolved in 3 ml of pyridine and 200 mg of acetic anhydride. After 12 h was the solution poured into water, the product taken up in ethyl acetate and the extract shaken with dilute hydrochloric acid and then with water. After drying the solvent was removed by distillation, and the syrupy residue crystallized within two days; yield 180 mg (70%), m.p. 63–64°C (light petroleum), $[\alpha]_D$ −13·7° (*c* 0·8; chloroform). For $C_{11}H_{16}F_2O_5$ (266·2) calculated: 49·62% C, 6·03% H, 14·30% F; found: 49·75% C, 5·97% H, 14·43% F.

1,6-Dideoxy-1,6-difluoro-D-fructose (*III*)

1 g of compound *IV* in 90 ml of 1% aqueous solution of *p*-toluenesulfonic acid was heated 3 h on a boiling water bath and then poured on a column of Amberlite IR 45. According to thin layer chromatography (benzene–methanol 9 : 1) did the neutral solution contain the starting compound (R_F 0·6) not even in traces, and contained only the compound with R_F 0·15. The column was washed with water, the aqueous solutions were combined, shaken with charcoal, filtered and evaporated *in vacuo*. Thereafter remained 750 mg (90%) of a syrup, $[\alpha]_D$ −12·5° (*c* 0·6; water). In paper chromatography (Whatman No 1, solvent system 1-butanol–water, detection with ammoniacal silver solution) it had an R_F value of 0·55. 2-Deoxy-2-fluoro-D-glucose[2] and 2,4-dideoxy-2,4-difluoro-D-glucose[2] have under the same conditions an R_F of 0·25 and 0·46, respectively. On oxidation with periodate[18] 1 mol of compound *III* consumes three mol of the reagent, and this almost immediately. For $C_6H_{10}F_2O_4$ (184·1) calculated: 39·14% C, 5·47% H, 20·64% F; found: 39·21% C, 5·69% H, 20·08% F.

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

0·45 g of the syrupy compound *III* were heated for 2½ h on a boiling water bath with 10 ml of acetic anhydride and 1 g of anhydrous sodium acetate. The reaction mixture was then poured into water, precipitating 0·3 g (45%) of crystals which, recrystallized from ether, had m.p. 102 to 103°C, $[\alpha]_D$ +60° (*c* 0·8; chloroform). For $C_{12}H_{16}F_2O_7$ (310·1) calculated: 46·45% C, 5·16% H, 12·26% F; found: 46·42% C, 5·11% H, 12·58% F.

4-O-Acetyl-2,3-O-isopropylidene-1,6-di-O-*p*-toluenesulfonyl-β-D-fructofuranose (*VII*)

6 g of compound *I* in 45 ml of pyridine were treated with 24 ml of acetic anhydride at room temperature. After 24 h was the mixture poured in 100 ml ice water. The deposited syrup was taken up in chloroform, dried over calcium chloride, and the chloroform after filtration removed by distillation. The remaining syrup was then dissolved in methanol, and after treating with a few drops of water (to the ensuing turbidity) was the solution put in the refrigerator, where a solid product deposited which was recrystallized from methanol. In this way were obtained 5·3 g (83%) of product *VII*; m.p. 80–82°C, $[\alpha]_D$ +20° (*c* 3·0; chloroform). For $C_{25}H_{30}O_{11}S_2$ (570·6) calculated: 52·68% C, 5·13% H, 11·29% S; found: 52·76% C, 5·31% H, 11·57% S.

4,6-Di-O-acetyl-2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructofuranose (*VIII*)

To 2 g of compound *I* in 20 ml of acetic anhydride were added 1·5 g of anhydrous potassium acetate, and the mixture was heated under reflux for 4 h. Then was the acetic anhydride distilled off *in vacuo*, the residue treated with water and extracted with ether. The ethereal extract was shaken with potassium hydrogen carbonate solution and water, decolourized with charcoal, dried, and then evaporated under reduced pressure, affording 1·4 g (80%) of a syrup, $[\alpha]_D$ +31° (*c* 1·02; chloroform). For $C_{20}H_{26}O_{10}S$ (458·2) calculated: 52·40% C, 5·67% H, 6·98% S; found: 52·29% C, 5·75% H, 7·29% S.

2,3-O-Isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructofuranose (*IX*)

Compound *VIII* was deacetylated in the usual manner under the catalysis of sodium methoxide. Recrystallization of the crude product from ether–light petroleum yielded crystals, m.p. 94·5 to 95·5°C, $[\alpha]_D$ +35° (*c* 1·03; chloroform). For $C_{16}H_{22}O_8S$ (374·2) calculated: 51·33% C, 5·88% H, 8·55% S; found: 51·21% C, 6·05% H, 8·48% S.

6-O-Benzoyl-2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-β-D-fructofuranose (*X*)

2·1 g of compound *I* were refluxed with a solution of 0·6 g of sodium benzoate in 15 ml dimethylformamide for 2 h. After diluting the solution with 100 ml of chloroform and extracting with 30 ml of water the aqueous layer was shaken twice with 20 ml of chloroform. The chloroformic layers were combined, shaken with 25 ml of water, dried, and the solvent removed by distillation. The remaining syrup was dissolved in benzene, boiled with charcoal, and run through a short column of alumina. The residue was crystallized from ethanol to afford 1·2 g (64%) of compound *X*, m.p. 130–131°C, $[\alpha]_D$ +27° (*c* 0·82; chloroform). For $C_{23}H_{26}O_9S$ (478·0) calculated: 57·74% C, 5·44% H, 6·68% S; found: 57·88% C, 5·55% H, 6·59% S.

2,3,4,5-Di-O-isopropylidene-1-O-*p*-nitrobenzenesulfonyl-β-D-fructopyranose (*XII*)

To a solution of 5·2 g of 2·3 : 4,5-di-O-isopropylidene-β-D-fructopyranose (*XIV*) in 40 ml of pyridine were added 5·3 g of *p*-nitrobenzenesulfonyl chloride at a temperature below 20°C. If in the course of the reaction not all went into solution, then was the reaction mixture warmed to about 30°C after having completed the addition. The reaction mixture was kept for 24 hours at room temperature and then decomposed with 200 ml of ice water. The deposited material was twice crystallized from methanol to give 3·3 g (40%) of compound *XII*, m.p. 117–118·5°C, $[\alpha]_D$ −172° (*c* 3·0; chloroform). For $C_{18}H_{23}NO_{10}S$ (477·5) calculated: 48·52% C, 5·21% H, 7·19% S, 3·15% N; found: 48·36% C, 5·32% H, 7·33% S, 3·20% N.

Attempted Preparation of 1-Deoxy-1-fluoro-2,3 : 4,6-di-O-isopropylidene-α-L-sorbofuranose

10 g of 2,3 : 4,6-Di-O-isopropylidene-1-O-*p*-toluenesulfonyl-α-L-sorbofuranose (*XV*) were refluxed under nitrogen with a solution of 5 g KF in 100 ml of ethylene glycol. After diluting, the reaction mixture was extracted with chloroform, the extract dried and evaporated. The residue was recrystallized from ether–light petroleum, to give a compound with a yield of approximately 60%, m.p. 118·5—120°C, $[\alpha]_D$ +15° (*c* 1·0; chloroform), corresponding by its properties with the already earlier described[19] 2,3-O-isopropylidene-1-O-*p*-toluenesulfonyl-α-L-sorbofuranose (*XVI*).

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