THE SYNTHESIS OF 6-AMINO-2,6-DIDEOXY-2-FLUORO-D-GLUCOSE*

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Reaction of methyl 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*I*) with sodium azide in dimethylformamide gives azide derivative *II* which after deacetylation, catalytic reduction, and hydrolysis affords 6-amino-2,6-dideoxy-2-fluoro-D-glucose hydrochloride (*V*). Attempts at the introduction of a fluorine atom into position $C_{(6)}$ instead of bromine, using the treatment of compound *I* with potassium fluoride in ethylene glycol, led to the formation of 3,6-anhydro derivative *X*, while when compound *I* was treated with potassium fluoride in dimethylformamide or also tetrabutylammonium fluoride in acetonitrile the unsaturated derivative *XII* was formed.

In past years a series of deoxyfluorinated derivatives of monosaccharides was prepared, many of which were submitted to biochemical investigations[1,2]. As it may be reasonably supposed that the deoxy fluorinated derivatives of amino sugars – up to now only sporadically described in the literature[3,4] – will also be interesting from the biological point of view, we decided to carry out the preparation of the hydrochloride of 6-amino-2,6-dideoxy-2-fluoro-D-glucose (*V*) which is a fluorinated analogue of a part of the molecule of the antibiotic kanamycin.

The starting substance for this synthesis was 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranosyl bromide which we obtained – alternatively to the original method of preparation[5] – by cleavage of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose[6] with hydrogen bromide in a mixture of acetic anhydride and acetic acid, without a previous hydrogenolysis off of the O-benzyl group. From 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranosyl bromide we prepared methyl 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*I*) in the manner described[5]. Substitution of its bromine atom at $C_{(6)}$ by the amino group was carried out indirectly *via* 6-azido derivative *II* which we obtained from compound *I* under the effect of sodium azide in dimethylformamide. The presence of the azido group in methyl 3,4-di-O-acetyl-6-azido-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*II*) followed both from the specific detection on a thin-layer plate[7]

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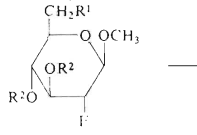
and from the IR spectrum. Compound *II* gave on deacetylation with sodium methoxide in methanol crude syrupy methyl 6-azido-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*III*) the reduction of which with Raney nickel afforded methyl 6-amino-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*IV*).

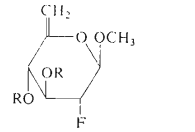
The inductive effect of the electronegative fluorine atom on $C_{(2)}$ manifests itself in compound *IV*, in agreement with previous findings[5,6], by substantially more difficult hydrolysis of the glycosidic group. It could be carried out only when 6M hydrochloric acid at 100°C was used. The use of 5% hydrochloric acid could not bring about a complete hydrolysis even after 10 hours' heating at 130°C in a sealed tube; in addition to this it was accompanied by degradation. The hydrolytically obtained 6-amino-2,6-dideoxy-2-fluoro-D-glucose hydrochloride (*V*) was converted to 6-acetamido-1,3,4-tri-O-acetyl-2,6-dideoxy-2-fluoro-D-glucose (*VI*) under the effect of acetic anhydride in the presence of anhydrous sodium acetate; its unsharp melting point indicates the presence of two anomers.

An alternative preparation of compound *V* was carried out by hydrolysis of glucoside *III* with 6M hydrochloric acid to 6-azido-2,6-dideoxy-2-fluoro-D-glucose (*VII*) and its subsequent catalytic reduction on palladium on charcoal in ethanol, containing 5% of hydrogen chloride. Compound *V* may be also obtained from 1,3,4-tri-O-acetyl-



I, $R^1 = Br$, $R^2 = Ae$
II, $R^1 = N_3$, $R^2 = Ac$
III, $R^1 = N_3$, $R^2 = H$
IV, $R^1 = NH_2$, $R^2 = H$

V, $R^1 = NH_3Cl$, $R^2 = H$
VI, $R^1 = NHAc$, $R^2 = Ac$
VII, $R^1 = N_3$ $R^2 = H$
VIII, $R^1 = Br$, $R^2 = Ac$
IX, $R^1 = N_3$, $R^2 = Ac$



XII, R = Ac

X, R = H
XI, R = Ac

-6-bromo-2,6-dideoxy-2-fluoro-D-glucopyranose[5] (*VIII*) *via* 1,3,4-tri-O-acetyl-6-azido-2,6-dideoxy-2-fluoro-D-glucopyranose (*IX*), which – according to the unsharp melting point – is evidently a mixture of anomers and which on deacetylation affords compound *VII*.

Of the three approximately equal methods of preparation of compound *V* mentioned here we gave preference to the first one, *i.e.* $I \rightarrow II \rightarrow III \rightarrow IV \rightarrow V$.

In addition to the preparation of aminofluorinated derivative *V* we also investigate in this paper the effect of potassium fluoride in boiling ethylene glycol on compound *I*. In the course of this reaction the substitution of the fluorine atom for the bromine atom at $C_{(6)}$ did not take place, but methyl 3,6-anhydro-2-deoxy-2-fluoro-β-D-glucoside (*X*) was formed, very probably with a pyranose structure. The formation of 3,6-anhydro cycle evidently takes place by base catalysis with fluoride ions, which enables deacetylation and the formation of an alkoxide ion at $C_{(3)}$ which then causes a nucleophilic attack at $C_{(6)}$ carbon. The presence of a free hydroxyl in compound *X* follows from its acetylation to methyl 4-O-acetyl-3,6-anhydro-2-deoxy-2-fluoro--β-D-glucoside (*XI*). If potassium fluoride in dimethylformamide is employed compound *I* gives according to thin-layer chromatography a mixture of three products of R_F 0·70, 0·30 and 0·13, of which the first distinctly prevails. All three can be well detected with alkaline potassium permanganate so that it may be supposed that dehydrobromination took place during the reaction with fluoride ions, under formation of a C=C double bond. In agreement with this the compound of R_F 0·70 was assigned the structure of methyl 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-β-D-*xylo*-hex-5-enopyranoside (*XII*) on the basis of its analysis and IR spectrum. On reaction of compound *I* with tetrabutylammonium fluoride in acetonitrile a mixture of three compounds is formed, having also R_F values 0·70, 0·30 and 0·13. Identity of compound of R_F 0·70 with compound *XII* from the preceding reaction was proved by its IR spectrum. According to IR spectrum the compound of R_F 0·13 does not contain acetyl groups, but it does contain hydroxyls and a C=C bond. As it is chromatographically identical with the product obtained on reaction of sodium methoxide in methanol with compound *XII* we suppose that it is the deacetylated product of compound *XII*. Similar results were also obtained by Pazourek[8] who obtained on reaction of methyl 3-O-acetyl-6-bromo-2,4,6-trideoxy-2,4-difluoro-β-D-glucopyranoside with potassium fluoride in boiling ethylene glycol the corresponding 3,6-anhydro derivative, while when using potassium fluoride in dimethylformamide or tetrabutylammonium fluoride in acetonitrile he prepared the corresponding 5,6-unsaturated derivative.

EXPERIMENTAL

The melting points were determined on a micro melting point Boetius apparatus, the optical rotations were measured on an automatic polarimeter Bendix–Ericsson, type 143 A, at 25°C. The infrared spectra were measured in chloroform ($c = 0{\cdot}5-1{\cdot}0\%$) on a UR 20 instrument

(Zeiss, Jena). The course of the reactions was followed by thin layer chromatography on silica gel according to Stahl, 5—20 μ particle size and about 0·2 mm layer thickness. Detections were carried out with 50% sulfuric acid and carbonisation. The solvents were distilled off in a vacuum rotary evaporator, between 20 to 70°C. The solutions were dried over anhydrous magnesium sulfate. The potassium fluride used was a dihydrate.

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

5 g of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose[6] in 15 ml of acetic anhydride and 60 ml of a 39% solution of anhydrous hydrogen bromide in acetic acid was allowed to stand at 20°C for 70 hours and it was then heated for 2·5 hours at 70°C and the solvent distilled off. The residual syrup was dissolved in 100 ml of chloroform, the solution was washed, shaken with two 20 ml portions of a saturated aqueous solution of sodium hydrogen carbonate and water. After drying and filtration with charcoal the solvent was distilled off. After recrystallisation from ethanol 4·8 g (62%) of product were obtained, m.p. 139—141°C, $[\alpha]_D$ +210° (0·6; chloroform), in agreement with the literature[5].

Methyl 3,4-di-O-acetyl-6-azido-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*II*)

A mixture of 4 g of methyl 3,4-di-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-β-D-glucopyranoside[5] (*I*), 2 g of sodium azide, and 100 ml of dimethylformamide was heated at 100°C for 3 hours. After pouring it into 200 ml of water the mixture was extracted with five 50 ml portions of chloroform. The combined extracts were washed with 20 ml of water, dried and filtered with charcoal. The residue after evaporation of the solvent gave on crystallisation from a mixture of ether and light petroleum 2·8 g (79%) of compound *II*, m.p. 97—98°C, $[\alpha]_D$ +7° (0·7; chloroform). IR spectrum: $\nu(N_3)$ 2115 cm^{-1}, $\nu(OCOCH_3)$ 1760 cm^{-1}. For $C_{11}H_{16}FN_3O_6$ (305·3) calculated: 43·28% C, 5·28% H, 6·22% F, 13·76% N; found: 43·38% C, 5·03% H, 6·35% F, 13·80% N.

Methyl 6-Amino-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*IV*)

Two grams of compound *II* were deacetylated with sodium methoxide in methanol, affording 1·44 g (98%) of syrupy methyl 6-azido-2,6-dideoxy-2-fluoro-β-D-glucopyranoside (*III*). One gram of compound *III* in 10 ml of methanol was hydrogenated on Raney nickel at room temperature and normal pressure. After two hours the reaction mixture was filtered and the solvent distilled off. The residue was crystallised from methanol–benzene giving 0·7 g (80%) of compound *IV*, m.p. 183—185°C (decom.), $[\alpha]_D$ −20° (0·8; water). For $C_7H_{14}FNO_4$ (195·2) calculated: 43·07% C, 7·23% H, 9·73% F, 7·17% N; found: 43·24% C, 7·32% H, 9·58% F, 7·28% N.

1,3,4-Tri-O-acetyl-6-azido-2,6-dideoxy-2-fluoro-D-glucose (*IX*)

1,3,4-Tri-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-D-glucose[5] (*VIII*) (0·9 g) and 1 g of sodium azide in 8 ml of dimethylformamide were heated at 60—70°C and stirred for 5 hours. After pouring the mixture into 50 ml of ice-cold water the precipitated material was dissolved in chloroform and after drying of the solution the solvent was distilled off. The residue after recrystallisation from a mixture of ether and methanol gave 0·5 g (70%) of compound *IX*, m.p. 108—123°C, $[\alpha]_D$ +109° (0·7; chloroform). For $C_{12}H_{16}FN_3O_7$ (333·3) calculated: 43·25% C, 4·84% H, 5·70% F, 12·61% N; found: 43·48% C, 4·93% H, 5·63% F, 12·56% N.

6-Azido-2,6-dideoxy-2-fluoro-D-glucose (*VII*)

a) Half a gram of compound *III* in 5 ml of 6M-HCl was heated on a boiling water bath for 3 hours. After distilling off of the acid 10 ml of water were added and the distillation repeated. This procedure was repeated twice more. Before the last distillation the solution was filtered with charcoal. The residual syrup of *VII* (0·42 g; 89%) was used directly for the preparation of compound *V*.

b) Half a gram of compound *IX* was deacetylated with sodium methoxide in methanol. The obtained syrup (0·30 g; 96%) was according to thin-layer chromatography (chloroform–methanol, 10 : 1) identical with the product obtained under *a*); both compounds have the same R_F value, 0·28.

Hydrochloride of 6-Amino-2,6-dideoxy-2-fluoro-D-glucose (*V*)

a) Compound *IV* (0·6 g) in 5 ml of 6M-HCl was heated in a boiling water bath for 4 hours. The acid was distilled off and the residue additioned three times with 15 ml of water and evaporated. Before the last distillation the solution was filtered with charcoal. The residual syrup (0·48 g; 72%) crystallised out on addition of methanol. Its R_F value in paper chromatography on Whatman No 1 paper (ethyl acetate–pyridine–water–acetic acid, 5 : 5 : 3 : 1) was 0·44 (the R_F value of 2-amino-2-deoxy-D-glucose hydrochloride is under the same conditions 0·34). About 185°C decomposition takes place without previous melting, $[\alpha]_D$ $+27° \rightarrow 40°$ (100 min, 0·7 in water). Reaction with ninhydrin is positive. For $C_6H_{13}ClFNO_4$ (217·6) calculated: 33·11% C, 6·02% H, 16·29% Cl, 8·73% F, 6·44% N; found: 33·15% C, 6·06% H, 16·23% Cl, 8·30% F, 6·46% N.

b) Compound *VII* (0·3 g) was hydrogenated in 3 ml of ethanol containing 5% of anhydrous hydrogen chloride, on 0·2 g of 5% palladium on charcoal. The reaction was carried out at normal pressure and room temperature for 12 hours. After filtration off of the catalyst the solution was evaporated and the residue additioned twice with 10 ml of water and evaporated after each addition. Before the last distillation the solution was filtered with charcoal. The remaining syrup (0·25 g; 78%) crystallised and it was found identical with the product prepared under *a*).

6-Acetamido-1,3,4-tri-O-acetyl-2,6-dideoxy-2-fluoro-D-glucose (*VI*)

Compound *V* (100 mg) was acetylated with acetic anhydride and anhydrous sodium acetate After recrystallisation 125 mg (78%) of compound *VI* were obtained, m.p. 190—196°C (sublimation begins at 160°C), $[\alpha]_D$ $+54°$ (0·45; chloroform). For $C_{14}H_{20}FNO_8$ (349·3) calculated: 48·14% C, 5·77% H, 5·44% F, 4·01% N; found: 48·20% C, 5·84% H, 5·48% F, 3·89% N.

Methyl 3,6-Anhydro-2-deoxy-2-fluoro-β-D-glucoside (*X*)

Compound[5] *I* (0·9 g) and 1 g of potassium fluoride were refluxed with 12 ml of ethylene glycol for 4 hours. After cooling, the mixture was diluted with 50 ml of water and extracted continually with 70 ml of ethyl acetate. The extract was washed with 10 ml of saturated sodium hydrogen carbonate solution and 10 ml of water. Both the hydrogen carbonate and water washings were reextracted with two 20 ml portions of ethyl acetate, the extracts were pooled, dried and filtered through charcoal and silica gel. Both adsorbents were washed with ethyl acetate and the combined filtrates were evaporated. The residual syrup was chromatographed on silica gel (benzene–acetone 15 : 1). The fraction of R_F 0·26 contained 0·3 g of syrup which crystallised after prolonged standing. Recrystallisation gave 0·2 g (44%) of compound *X*, m.p. 48—50°C, $[\alpha]_D$ $-169°$ (0·7, chloroform).

IR spectrum: ν(OH) 3 610 cm^{-1}. For $C_7H_{11}FO_4$ (178·2) calculated: 47·19% C, 6·22% H, 10·66% F; found: 46·97% C, 6·30% H, 10·73% F.

Methyl 4-O-Acetyl-3,6-anhydro-2-deoxy-2-fluoro-β-D-glucoside (*XI*)

Acetylation of 100 mg of compound *X* was carried out with acetic anhydride and anhydrous sodium acetate. After crystallisation of the product from a mixture of ether and methanol 90 mg (76%) of compound *XI* were obtained, m.p. 109–111°C, $[\alpha]_D$ −115° (0·4, chloroform). For $C_9H_{13}FO_5$ (220·2) calculated: 49·09% C, 5·95% H, 8·62% F; found: 49·30% C, 6·01% H, 8·49% F.

Methyl 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-β-D-*xylo*-hex-5-enoside (*XII*)

a) Compound[5] *I* (0·4 g) was refluxed with 0·5 g of potassium fluoride in 10 ml of dimethylformamide for three hours. The mixture was poured into 20 ml of water and extracted with five 20 ml portions of ethyl acetate. The extract was dried and filtered through a layer of charcoal and the solvent distilled off. The residual syrup contained according to thin-layer chromatography in benzene–acetone (10 : 1) in addition to the main product *XII* of R_F 0·70 also a lesser amount of admixtures of R_F 0·38 and 0·13. After chromatography on a silica gel column (benzene–acetone, 15 : 1) 0·25 g of syrupy product *XII* were obtained which after distillation (0·05 Torr, 120°C bath temperature) gave 0·2 g (65%) of a syrup, $[\alpha]_D$ −27° (0·7, chloroform). IR spectrum: ν($OCOCH_3$) 1 765 cm^{-1}, ν(CH_2=C) 1 675 cm^{-1}. For $C_{11}H_{15}FO_6$ (262·2) calculated: 50·38% C, 5·76% H, 7·24% F; found: 50·11% C, 5·85% H, 7·28% F.

b) Compound[5] *I* (0·5 g) and tetrabutylammonium fluoride[9] (2 g) in acetonitrile (10 ml) were refluxed for 2 hours. Thin-layer chromatography in benzene–acetone 10 : 1 revealed the presence of compounds of R_F 0·70, 0·38 and 0·13. The reaction mixture was poured into 10 ml of water and extracted four times with 20 ml of ethyl acetate. The combined extracts were dried, filtered through charcoal and evaporated. After chromatography on a silica gel column (benzene–acetone, 15 : 1) 0·25 g (65%) of syrupy product *XII* were obtained the identity of which with the product prepared under *a*) was proved by their IR spectra. Further, 0·1 g of the product of R_F 0·13 (in benzene–acetone 10 : 1) or 0·65 (in chloroform–methanol 10 : 1) were obtained, which according to its IR spectrum contained hydroxyl groups (3 450 and 3 610 cm^{-1}) and a C=C double bond (1 675 cm^{-1}), but no acetyl groups. It is chromatographically identical with the most polar product of the reaction mixture obtained under *a*) and with the product obtained by deacetylation of compound *XII* with sodium methoxide in methanol.

REFERENCES

1. Podešva J., Pacák J.: Chem. listy *67*, 785 (1973).
2. Foster A. B., Westwood J. H.: Pure Appl. Chem. *35*, 147 (1973).
3. Shulman M. L., Khorlin A. Y.: Carbohydrate Res. *27*, 141 (1973).
4. Pacák J., Drašar P., Štropová D., Černý M., Buděšínský M.: This Journal *38*, 3936 (1973).
5. Černý M., Přikrylová V., Pacák J.: This Journal *37*, 2978 (1972).
6. Pacák J., Podešva J., Točík Z., Černý M.: This Journal *37*, 2589 (1972).
7. Černý M., Elbert T., Pacák J.: This Journal *39*, 1752 (1974).
8. Pazourek K.: *Thesis*. Charles University, Prague 1972.
9. Foster A. B., Hems R.: Methods in Carbohydrate Chem. *6*, 197 (1972).

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