FLUORINATED DERIVATIVES OF 1,6-ANHYDRO-β-D-*ribo*-HEXOPYRANOS-3-ULOSE*

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Received March 24th, 1976

Oxidation of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (*I*) with ruthenium tetroxide and of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVI*) with chromium trioxide gave 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-*ribo*-hexopyranos-3-ulose (*II*) or the hydrate of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-*ribo*-hexopyranoses-3-ulose (*XVII*). Both compounds were successfully converted to corresponding 2-deoxy-2-fluoro- or 2,4-dideoxy--2,4-difluoro derivatives of 1,6-anhydro-β-D-allopyranose and their structure proved. The paper indicates new possibilities of synthesis of 2-deoxy-2-fluoro-D-allose and 2,4-dideoxy-2,4-difluoro-D-allose.

Aldosuloses and their derivatives can be prepared by oxidation[1,2] of suitably protected aldoses and they can be used as intermediates in various kinds of syntheses. For this reason we decided to carry out the oxidations of some fluorinated derivatives of 1,6-anhydro-β-D-glucopyranose[3] to corresponding fluorinated derivatives of deoxyaldosuloses and to investigate their synthetic use.

One of the starting compounds was 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β--D-glucopyranose (*I*). The preparation of this compound was carried out according to literature[3]. We investigated its oxidation to 1,6-anhydro-4-O-benzyl-2-deoxy--2-fluoro-β-D-*ribo*-hexopyranos-3-ulose (*II*) with various reagents, such as chromium trioxide, dimethyl sulfoxide with acetic anhydride, or ruthenium tetroxide. The last one proved to be the best. This reaction gave a compound which corresponded in its properties to aldosulose *II*; its IR spectrum indicates the presence of a free carbonyl group ($\tilde{\nu} = 1740\ cm^{-1}$). On reduction with sodium borohydride in methanol it gave a product which displayed a characteristic absorption of the hydroxyl group ($\tilde{\nu} = 3460\ cm^{-1}$). As the compound obtained in this manner differed distinctly from 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (*I*) it could be assumed that it was 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-allopyranose (*III*). This was shown by catalytic debenzylation of *III* in which 1,6-anhydro-2-deoxy-

* Part XXVIII in the series Syntheses with Anhydro Sugars; Part XXVII: This Journal *41*, 2942 (1976). This paper comprizes a part of the results of the thesis by M. Braunová and D. Štropová (Charles University).

-2-fluoro-β-D-allopyranose (*IV*) was formed, which was identical in its melting point and specific rotation with the product prepared earlier[4] from 2-deoxy-2-fluoro-D-allose (*V*) in reaction with acids. The reduction of compound *II* to a D-allose derivative is in agreement with Cram's rule and it corresponds according to its reaction course to the reduction of 1,6-anhydro-4-O-benzyl-2-O-*p*-toluenesulfonyl-β-D-*ribo*-hexopyranos-3-ulose to 1,6-anhydro-4-O-benzyl-2-O-*p*-toluenesulfonyl-β-D-allopyranose[2].

As according to preliminary experiments the anhydro ring of *IV* can be cleaved to fluorinated D-allose *V* (with 1% aqueous *p*-toluenesulfonic acid at 170°C), the reaction sequence $I \rightarrow II \rightarrow III \rightarrow IV \rightarrow V$ represents a novel and unambiguous procedure for the synthesis of 2-deoxy-2-fluoro-D-allose (*V*).

The *cis* arrangement of vicinal hydroxyls on carbon atoms $C_{(3)}$ and $C_{(4)}$ in compound *IV* was further confirmed by the preparation of its O-isopropylidene derivative *VI* under the effect of acetone and anhydrous copper sulfate and sulfuric acid as catalyst. Tosylation of compound *I* and *III* with *p*-toluenesulfonyl chloride in pyridine gave corresponding 3-O-tosyl derivatives *VII* and *VIII*. With 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-3-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VII*) an unsuccessful experiment was carried out aiming at the substitution of the tosyloxy group by an azide group, using sodium azide in dimethylformamide as reagent. Catalytic debenzylation of *VII* took place under formation of 1,6-anhydro-2-deoxy-2-fluoro-3-O-*p*-toluenesulfonyl-β-D-glucopyranose (*IX*) which is a suitable intermediate for the preparation of 1,6 : 3,4-dianhydro-2-deoxy-2-fluoro-β-D-allopyranose.

In an effort to prepare 1,6-anhydro-2-deoxy-2-fluoro-β-D-*ribo*-hexopyranos-3-ulose (*X*) compound *II* was submitted to catalytic debenzylation on palladium at a mildly elevated temperature and normal pressure. However, the required product *X* could not be obtained in a pure form but a mixture of substances was formed which could not be separated. The presence of compound *X* in this mixture, however, follows from the fact that after the reduction of this mixture with sodium borohydride and subsequent isopropylidenation of the reduction products with acetone in the presence of anhydrous copper sulfate a product was obtained which was identical with product *VI*, obtained by isopropylidenation of 1,6-anhydro-2-deoxy-2-fluoro-β-D-allopyranose (*IV*).

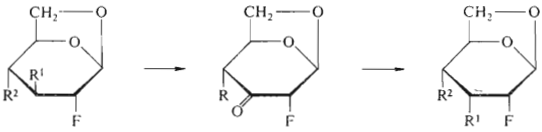
By acetolysis of compound *II* with acetic anhydride and perchloric acid a product was obtained which according to its mass spectrum did not contain a benzyl group (the abudance of ions m/e 91 and other fragments of the aromatic ring is negligible). This means that not only the opening of the 1,6-anhydro ring took place in the course of acetolysis, but debenzylation as well. However, this fact is known from literature[5]. According to elemental analysis, IR spectra and specific rotation of the product of acetolysis we assume that 1,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-*ribo*-hexopyranos-3-ulose (*XI*) is formed under these conditions.

Attempts at the preparation of an oxime by reacting *II* with hydroxylamine were unsuccessful. In contrast to this the reaction of *II* with methyl magnesium iodide led to the isolation of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-3-C-methyl-β-D-allopyranose (*XII*). Its formation is indicated by the disappearance of the carbonyl vibration in the IR spectrum under simultaneous appearance of a vibration corresponding to a hydroxyl ($\tilde{\nu} = 3600\ cm^{-1}$). Catalytic debenzylation of the addition product *XII* gives 1,6-anhydro-2-deoxy-2-fluoro-3-C-methyl-β-D-allopyranose (*XIII*) which can be converted to the corresponding O-isopropylidene derivative, *i.e.* 1,6-anhydro-2-deoxy-2-fluoro-3,4-O-isopropylidene-3-C-methyl-β-D-allopyranose (*XIV*). The addition of the Grignard reagent to 3-ulose *II* took place from the sterically less hindered side, *i.e.* from the side opposite to that where the benzyloxy group and the fluorine atom are located. The sterical course of this addition agrees with our earlier experiences concerning the addition of methylmagnesium iodide to 1,6-anhydro-2,4-di-O-*p*-toluenesulfonyl-β-D-*ribo*-hexopyranos-3-ulose[6].

Preliminary we have found that the cleavage of the 1,6-anhydro ring in compounds *XII* and *XIII* can be carried out by their heating with 5% aqueous *p*-toluenesulfonic acid solution in a sealed tube at 165°C for 10 hours. According to paper chromatographic analysis both compounds afford the same product, which means that in the case of compound *XII* the splitting off of the benzyl group takes place as well. The acetylation of compound *XII* to 3-O-acetyl-1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro--3-C-methyl-β-D-allopyranose (*XV*) could not be carried out with acetic anhydride in pyridine, but it could with acetic anhydride in the presence of *p*-toluenesulfonic acid.

When treated with pyridine, *II* is isomerized, which is in agreement with analogous results in our preceding paper[2]; the specific rotation $[\alpha]_D$ of a pyridine solution of *II* decreased from $-17{\cdot}3°$ to $-80°$ within several hours and then remained unchanged. The solution contained a mixture of compounds according to TLC.

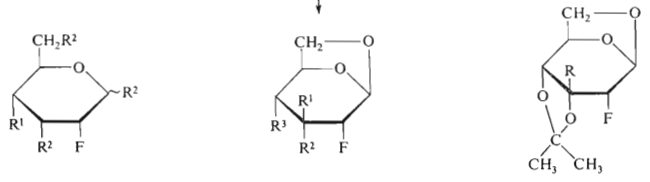
The second compound which we tried to oxidize to the corresponding 1,6-anhydroaldosulose was 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVI*). We oxidized this compound, also prepared from 1,6 : 3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose[3], with various reagents, as for example chromium trioxide in water, in acetic acid or in pyridine, further with dimethyl sulfoxide in acetic anhydride, and eventually with ruthenium tetroxide. Best results and an individual reaction product was obtained with chromium trioxide in water or ruthenium tetroxide. We used chromium trioxide and destroyed its excess with sulfur dioxide after the reaction was complete; after the working up of the reaction mixture the hydrate of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-*ribo*-hexopyranos-3-ulose (*XVII*) was obtained, the structure of which follows from its ^{1}H-NMR spectrum (measured in hexadeuteriodimethyl sulfoxide). The presence of geminal hydroxyls with δ 6·28 and δ 6·52 was demonstrated, the signals of which disappear in the presence of CH_3. .COOD. The configuration of F−4 follows from the values of coupling constants



I, R^1 = OH, R^2 = OBn
VII, R^1 = OTs, R^2 = OBn
IX, R^1 = OTs, R^2 = OH
XVI, R^1 = OH, R^2 = F
XXII, R^1 = OTs, R^2 = F

II, R = OBn
X, R = OH
XVIII, R = F

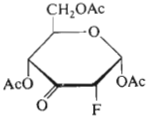
III, R^1 = OH, R^2 = OBn
IV, R^1 = R^2 = OH
VIII, R^1 = OTs, R^2 = OBn
XIX, R^1 = OH, R^2 = F
XXIII, R^1 = OTs, R^2 = F



V, R^1 = R^2 = OH
XX, R^1 = F, R^2 = OAc
XXI, R^1 = F, R^2 = OH

XII, R^1 = CH_3, R^2 = OH, R^3 = OBn
XIII, R^1 = CH_3, R^2 = R^3 = OH
XV, R^1 = CH_3, R^2 = OAc, R^3 = OBn
XVII, R^1 = R^2 = OH, R^3 = F

VI, R = H
XIV, R = CH_3



XI

Abbreviations:

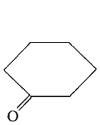
Ts = *p*-toluenesulfonyl
Bn = benzyl
Ac = acetyl

$J_{4,5}$ = 2·1 Hz, $J_{5,4F}$ = 9·6 Hz and $J_{6exo,4F}$ = 4·0 (*W* arrangement), and the configuration of F−2 from the value $J_{2,4}$ = 1·3 Hz (*W* arrangement). Other parameters also correspond to the assumed structure. In the IR spectrum of compound *XVII* in tetrachloromethane no carbonyl band was found, but in the 3592 cm^{-1} region a band corresponding to $\tilde{\nu}$(OH) was present.

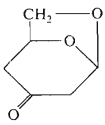
The formation of hydrate *XVII* instead of 1,6-anhydro-2,4-dideoxy-2,4-difluoro--β-D-*ribo*-hexopyranos-3-ulose (*XVIII*) is evidently caused mainly by the presence of fluorine atoms in both positions α next to the carbonyl group. It is well known that ketones substituted at these positions with several fluorine atoms exist in hydrated

form exclusively[7,8]. The reason for this is, of course, the fact that by hydration the molecule is freed from the thermodynamically infavourable cumulation of three positive partial charges (on the carbonyl carbon and in both α-positions). Intramolecular hydrogen bonds which are sterically possible betwen the hydroxyl groups and the oxygen atom of the 1,6-anhydro ring and the fluorine atoms also contribute to the stabilization of hydrate. Finally, it is also known that the D-*ribo* configuration of 1,6-anhydro-β-D-hexopyranos-3-ulose is sterically favourable for acetalization or hydration[9,10].

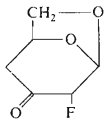
Hydrate *XVII* is chemically very poorly reactive so that it did not give an oxime on reaction with hydroxylamine, although, for example, 1,6-anhydro-3,4-O-isopropylidene-β-D-*lyxo*-hexofuranos-2-ulose[11] or the hydrate of 1,2 : 5,6-di-O-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[12] afford an oxime easily. Attempts at dehydration of *XVII* under various conditions were unsuccessful. Only when directly heated in the presence of a molecular sieve (Nalsit A4) *in vacuo* a small amount of liquid distilled off, the chloroform solution of which displayed intensive absorption at $\tilde{\nu} = 1765\ \mathrm{cm}^{-1}$. The shift of the carbonyl group stretching vibrations of the assumed ulose *XVIII* to higher frequency values with respect to cyclohexanone ($\tilde{\nu} \approx 1710\ \mathrm{cm}^{-1}$), when measured in non-polar solvents, corresponds not only to the different geometry of its six-membered ring (due to the introduction of 1,6-anhydro ring into the molecule of γ-pyrone the valence angle $C_{(2)}$—CO—$C_{(4)}$ is also changed, which results in a shift of the carbonyl vibrations to values laying between the values for cyclohexanone and cyclopentanone[13]), but also to an increase in the force constant of the bond under the effect of the presence of both fluorine atoms in positions α; (see Scheme 1).



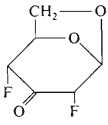
$\tilde{\nu} = 1711\ \mathrm{cm}^{-1}$
(lit. 13)



$\tilde{\nu} = 1730\ \mathrm{cm}^{-1}$
(lit. 9)



$\tilde{\nu} = 1745\ \mathrm{cm}^{-1}$
(lit. 14)



$\tilde{\nu} = 1765\ \mathrm{cm}^{-1}$

SCHEME 1

We tried to exchange the two geminal hydroxyl groups for two fluorine atoms by reacting hydrate *XVII* with phenylsulfur trifluoride ($C_6H_5SF_3$). The work with this reagent[15] in the laboratory is easier than with sulfur tetrafluoride[15], because in the latter case the operation must be done in a pressure bottle coated with special

steel. Phenylsulfur trifluoride was prepared according to Sheppard[16] from silver perfluoride (AgF_2) and diphenyl disulfide. When heating *XVII* with the mentioned reagent at 120°C in a teflon tube neither the introduction of the fluorine atoms at $C_{(3)}$ nor dehydration took place; unchanged hydrate *XVII* was detected in the reaction mixture. However, the reduction of *XVII* with sodium borohydride in ethanol was successful. It took place analogously as the reduction of compound *II*, in agreement with Cram's rule, under formation of 1,6-anhydro-2,4-dideoxy-2,4-difluoro--β-D-allopyranose (*XIX*). Its structure follows from elemental analysis, melting point, differing from that of D-*gluco* isomer, and from specific rotation which is very close to the value of 1,6-anhydro-β-D-allopyranose. The considerable similarity of the specific rotation values of 1,6-anhydrohexopyranoses and their fluorinated derivatives has been mentioned elsewhere[17].

The preparation of 2,4-dideoxy-2,4-difluoro-D-allose by hydrolysis of *XIX* has been tried by an earlier proved method[3], using a 1% aqueous solution of *p*-toluenesulfonic acid in a sealed tube at elevated temperature. In this case the hydrolysis did not take place even at 190°C. Therefore we cleaved the 1,6-anhydro ring with acetic anhydride under catalysis of perchloric acid. Thus 1,3,6-tri-O-acetyl-2,4-dideoxy-2,4-difluoro-D-allopyranose (*XX*) was obtained which after isolation and deacetylation according to Zemplén gave not completely pure 2,4-dideoxy-2,4-difluoro-D-allose (*XXI*).

Other fluorinated sugar derivatives were also prepared: reduction of 2,4-dideoxy--2,4-difluoro-D-glucose[3] with sodium borohydride gave 2,4-dideoxy-2,4-difluoro--D-glucitol, tosylation of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucose (*XVI*) and 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-allose (*XIX*) gave their corresponding 3-O-tosyl esters *XXII*, *XXIII*. According to expectation this esterification takes place in the case of D-allose derivative with an equatorial hydroxyl at $C_{(3)}$ distinctly faster than in the case of D-glucose derivative with an axial hydroxyl group.

EXPERIMENTAL

The melting points were measured on a Boëtius micromelting point apparatus; the optical rotation values were measured on an automatic Bendix Ericsson UK LTD polarimeter, Type 143 A, at 23–25°C. Thin-layer chromatography was carried out on silica gel G according to Stahl. Detection was carried out with 50% sulfuric acid and carbonization. The solvents used were anhydrous. Evaporations were carried out at temperatures up to 50°C on an automatic evaporator. IR-Spectra were measured in chloroform on a Zeiss UR Spectrophotometer unless stated otherwise.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose (*I*)

The compound prepared according to literature[3] had m.p. 80–81°C, $[\alpha]_D$ −40°; literature[3] gives m.p. 69°C and $[\alpha]_D$ −40°.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-*ribo*-hexopyranos-3-ulose (*II*)

Dihydrate of ruthenium dioxide (1 g) was added into a solution of 18·5 g of sodium periodate in 400 ml of water. The mixture was stirred until the ruthenium dioxide was converted to a yellow ruthenium tetroxide solution. The latter was extracted with five 50 ml portions of tetrachloromethane. The extract was dried over anhydrous magnesium sulfate and filtered, and 1 g of compound *I* dissolved in 2 ml of acetone was added to it. After 6 hours' stirring the starting compound disappeared from the reaction mixture according to thin-layer chromatography (benzene–acetone 9 : 1). The separated dihydrate of ruthenium dioxide was filtered off, the filtrate purified by filtration through a small column of silica gel and charcoal, and the solvents were evaporated. The residual oil (880 mg) crystallized out after several days' standing. It was recrystallized from ether–light petroleum. Yield 0·84 g (85%), m.p. 53–54°C, $[\alpha]_D$ −17° (*c* 0·6, chloroform). IR spectrum: $\tilde{\nu}$ (CO) 1740 cm^{-1}. UV spectrum: λ_{max} (CO) 208 nm (methanol). For $C_{13}H_{13}FO_4$ (252·2) calculated: 61·90% C, 5·19% H, 7·53% F; found: 61·89% C, 5·19% H, 7·51% F.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-allopyranose (*III*)

Compound *II* (0·5 g) was dissolved in 5 ml of methanol. After addition of a solution of 60 mg of sodium borohydride in 6 ml of methanol the mixture was allowed to stand at room temperature for 15 minutes; 2 ml of acetic acid were then added and the mixture evaporated. The residue was dissolved in methanol (5 ml) and the solvent evaporated. This procedure was repeated three times. After crystallization from chloroform–ether 350 mg (70%) of product were obtained, m.p. 95–97°C, $[\alpha]_D$ −80° (*c* 0·6, chloroform). IR spectrum: $\tilde{\nu}$ (OH) 3460 cm^{-1}. For $C_{13}H_{15}FO_4$ (254·3) calculated: 61·41% C, 5·95% H, 7·47% F; found: 61·39% C, 5·86% H, 7·52% F.

1,6-Anhydro-2-deoxy-2-fluoro-β-D-allopyranose (*IV*)

Compound *III* (300 mg) in 15 ml (96%) ethanol was hydrogenolysed in the presence of 150 mg of Pd on charcoal[18] (10%) at normal pressure and 40°C for 5 hours. After this period no starting compound was any longer present in the reaction mixture according to thin layer chromatography. After filtration and decolorization with charcoal the mixture was evaporated. After recrystalization from acetone–light petroleum 180 mg (92%) of product were obtained, m.p. 138–140°C, $[\alpha]_D$ −75° (*c* 0·6, water). Literature[4] gives m.p. 137–139°C, $[\alpha]_D^{22}$ −79° (*c* 1·0, water).

1,6-Anhydro-2-deoxy-2-fluoro-3,4-O-isopropylidene-β-D-allopyranose (*VI*)

Compound *IV* (100 mg) was dissolved in 7 ml of acetone, 60 mg of anhydrous copper sulfate and a drop of concentrated sulfuric acid were added and the mixture shaken for 2 days, until the starting compound disappeared (according to thin-layer chromatography in benzene–acetone 9 : 1). After filtration the reaction mixture was neutralized with aqueous sodium hydroxide and evaporated. The residue was dissolved in chloroform, dried over anhydrous magnesium sulfate and the solution evaporated. Crystallization was carried out from ether–light petroleum mixture. Yield 100 mg (80%), m.p. 130–132°C, $[\alpha]_D$ −84° (c 0·5, chloroform). For $C_9H_{13}FO_4$ (204·2) calculated: 52·93% C, 6·42% H, 9·30% F; found: 53·23% C, 6·62% H, 9·51% F.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-3-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VII*)

Compound *I* (1 g) was dissolved in 15 ml of pyridine, 2 g of *p*-toluenesulfonyl chloride were added to it, and the mixture allowed to stand for three days. When according to thin layer chro-

matography all starting material had reacted the mixture was poured into 100 ml of icy water. The separated crystals were filtered off and recrystallized from aqueous ethanol. Yield 1·2 g (75%), m.p. 116–117°C, $[\alpha]_D$ +48° (*c* 0·7, chloroform). For $C_{20}H_{21}FO_6S$ (408·4) calculated: 58·81% C, 5·17% H, 4·65% F, 7·85% S; found: 58·70% C, 5·19% H, 4·94% F, 7·82% S.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-3-O-*p*-toluenesulfonyl-β-D-allopyranose (*VIII*)

Compound *III* (100 mg) was dissolved in 1·5 ml of pyridine and 150 mg of *p*-toluenesulfonyl chloride were added. After 48 hours' standing the mixture was poured into 30 ml of icy water and the separated crystals were filtered off. After crystallization from aqueous ethanol 110 mg (69%) of a product melting at 158–159°C, $[\alpha]_D$ −25° (*c* 0·6, chloroform) were obtained. For $C_{20}H_{21}FO_6S$ (408·4) calculated: 58·81% C, 5·17% H, 4·65% F, 7·85% S; found: 58·92% C, 5·34% H, 5·01% F, 7·79% S.

1,6-Anhydro-2-deoxy-2-fluoro-3-O-*p*-toluenesulonyl-β-D-glucopyranose (*IX*)

The hydrogenolysis of compound *VII* (1 g) was carried out under catalysis with Pd on active charcoal[18] (10%) at normal pressure and 40°C. The reaction was over after 6 hours. After filtration and evaporation of the solvent a substance was obtained which after crystallization from ethanol–light petroleum gave 740 mg (95%) of product of m.p. 83–84°C, $[\alpha]_D$ −16° (*c* 0·6, chloroform). For $C_{13}H_{15}FO_6S$ (318·2) calculated: 49·23% C, 4·74% H, 5·96% F, 10·07% S; found: 49·30% C, 4·84% H, 6·11% F, 9·97% S.

Catalytic Hydrogenation of 1,6-Anhydro-4-O-benzyl 2-deoxy-2-fluoro-β-D-*ribo*-hexopyranos--3-ulose (*II*)

Compound *II* (200 mg) was dissolved in 10 ml of methanol and 100 mg of Pd on charcoal[18] (10%) was added to it. Hydrogenolysis was carried out at normal pressure and 40°C for 5 hours. After filtration of the catalyst 100 mg of sodium borohydride were added to the solution, and the mixture allowed to react for 15 minutes. Excess hydride was then decomposed with 1 ml acetic acid. According to thin layer chromatography (ethanol–dioxan–benzene–ammonia 8 : 40 : 50 : 5) the solution is a mixture of 1,6-anhydro-2-deoxy-2-fluoro-β-D-allopyranose (*IV*) (main component) and smaller quantities of 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose[3] and 1,6--anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-allopyranose (*III*). The presence of compound *IV* was proved by isopropylidenation of the mixture with 15 ml of acetone and 400 mg of anhydrous copper sulfate and a drop of sulfuric acid. After two days's shaking and then working up 80 mg of a compound of m.p. 129–130°C was obtained, which corresponds to that of 1,6-anhydro--2-deoxy-2-fluoro-3,4-O-isopropylidene-β-D-allopyranose (*VI*).

1,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-*ribo*-hexopyranos-3-ulose (*XI*)

Compound *II* (250 mg) and 2 ml of acetic anhydride containing 0·04 ml of aqueous 70% perchloric acid were allowed to stand at room temperature for 20 hours. After decomposition with water and neutralization with an aqueous solution of sodium carbonate the solution was extracted with chloroform. After drying of the extract with calcium chloride and decolorization with charcoal the solution was filtered and evaporated. The residue (200 mg of syrup) crystallized after addition of ether. After several crystallizations from ether–light petroleum mixture 90 mg (30%) of crystalls were obtained, melting at 115–119°C, $[\alpha]_D$ +113° (*c* 0·7, chloroform), IR spectrum: $\tilde{\nu}$(CO) 1745 cm^{-1} and 1760 cm^{-1}. For $C_{12}H_{15}FO_8$ (306·2) calculated: 47·06% C, 4·93% H, 6·20% F; found: 47·14% C, 4·98% H, 6·14% F.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-fluoro-3-C-methyl-β-D-allopyranose (*XII*)

A solution of compound *II* (0·6 g) in 10 ml of ether was added dropwise under cooling with ice and stirring into a solution obtained from 1·2 g of magnesium shavings, 60 ml of ether and 4 ml of methyl iodide and the mixture was stirred at room temperature for 2 hours. It was then poured into water, acidified with dilute hydrochloric acid and extracted with chloroform. The extract was washed with water until neutral, dried over calcium chloride and evaporated. The residue (400 mg) was crystallized from ethanol–light petroleum to give 350 mg (55%) of compound, m.p. 56–58°C, $[\alpha]_D$ −48° (*c* 0·5, chloroform); IR spectrum: $\tilde{\nu}$(OH) 3600 cm^{-1}. For $C_{14}H_{17}FO_4$ (268·3) calculated: 62·67% C, 6·39% H, 7·09% F; found: 62·89% C, 6·36% H, 7·27% F.

1,6-Anhydro-2-deoxy-2-fluoro-3-C-methyl-β-D-allopyranose (*XIII*)

Compound *XII* (300 mg) was dissolved in 8 ml of methanol, palladium on charcoal[18] (10%; 150 mg) was added and the mixture hydrogenated at normal pressure and 40°C for 3 hours. After filtration off of the catalyst and evaporation of the solvent the residue (160 mg) was crystallized from ethanol–light petroleum. Yield 140 mg (70%), m.p. 170–172°C, $[\alpha]_D$ −59° (*c* 0·7, chloroform). For $C_7H_{11}FO_4$ (178·2) calculated: 47·19% C, 6·23% H, 10·66% F; found: 47·31% C, 6·15% H, 10·73% F.

1,6-Anhydro-2-deoxy-2-fluoro-3,4-O-isopropylidene-3-C-methyl-β-D-allopyranose (*XIV*)

Anhydrous copper sulfate (40 mg) was added to a solution of *XIII* (80 mg) in 4 ml acetone and the mixture was shaken for one day. After filtration the filtrate was evaporated and the residue extracted with chloroform. The extract, dried over magnesium sulfate, was evaporated. The residue (95 mg) was crystallized from ether–light petroleum to yield 80 mg (82%) of pure compound, m.p. 68–70°C, $[\alpha]_D$ −52° (*c* 0·7, chloroform). For $C_{10}H_{15}FO_4$ (218·2) calculated: 55·03% C, 6·93% H, 8·70% F; found: 55·39% C, 6·88% H, 8·50% F.

3-O-Acetyl-1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-3-C-methyl-β-D-allopyranose (*XV*)

Compound *XII* (100 mg) was mixed with 3 ml of acetic anhydride and 50 mg of *p*-toluenesulfonic acid and then stirred at room temperature for one hour. The mixture was poured into a saturated aqueous solution of potassium hydrogen carbonate and extracted four times with 25 ml of chloroform. The combined extracts were washed with water and dried over anhydrous calcium chloride. After evaporation of the solvent the residue was crystallized from ethanol. Yield 110 mg (95%), m.p. 118–120°C, $[\alpha]_D$ −30° (*c* 0·7, chloroform); IR spectrum: $\tilde{\nu}$(CO) 1735 cm^{-1}. For $C_{16}H_{19}FO_5$ (310·3) calculated: 61·92% C, 6·17% H, 6·12% F; found: 61·96% C, 6·33% H, 6·21% F.

Hydrate of 1,6-Anhydro-2,4-dideoxy-2,4-difluoro-β-D-*ribo*-hexopyranos-3-ulose (*XVII*)

Chromium trioxide (6·6 g) in 10 ml of water was added to 1 g of 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*XVI*) and the mixture was heated at 60°C for 8 hours. The mixture was diluted with water to 50 ml volume and sulfur dioxide was introduced into it until the excess chromate ions were reduced to chromic ions. The solution was then heated to eliminate excess sulfur dioxide and then extracted continuously with ethyl acetate. The extract was evaporated. The residual product (0·85 g) was crystallized from ethyl acetate to give 0·66 g (60%) of fine needles, m.p. 119–120°C (sealed capillary), $[\alpha]_D$ −61° (*c* 0·8, water). Thin layer chromatography:

R_F (benzene–acetone 9 : 1) 0·08. For $C_6H_8F_2O_4$ (182·1) calculated: 39·57% C, 4·43% H, 20·86% F; found: 39·88% C, 4·42% H, 20·06% F. IR spectrum: $\tilde{\nu}$(OH) 3375–3460 cm^{-1} (nujol), $\tilde{\nu}$(OH) 3592 cm^{-1} (tetrachloromethane). ^{1}H-NMR spectrum (Varian HA-100, in hexadeuteriodimethyl sulfoxide, tetramethylsilane as internal reference, chemical shifts in δ-units (p.p.m.), coupling constants J in Hz): 5·49 H–1, $J_{1,2}$ = 2·2, $J_{1,2F}$ = 2·2; 4·07 H–2, $J_{1,2}$ = 2·2, $J_{2,2F}$ = 48, $J_{2,4}$ = 1·3; 4·23 H–4, $J_{4,5}$ = 2·1, $J_{4,4F}$ = 9·6, $J_{2,4}$ = 1·3; 4·73 H–5, $J_{4,5}$ = 2·1, $J_{5,4F}$ = 9·6, $J_{5,6endo}$ = 1·2, $J_{5,6exo}$ = 5·9; 4·03 H–6 endo, $J_{5,6endo}$ = 1·2, $J_{6endo,4F}$ = 1·0, $J_{6,6}$ = 7·2; 3·75 H–6 exo, $J_{5,6exo}$ = 5·9, $J_{6exo,4F}$ = 4·0, $J_{6,6}$ = 7·2; 6·28 and 6·52 HO (after addition of CH_3COOD it disappears).

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-β-D-allopyranose (*XIX*)

A 1% ethanolic sodium borohydride solution (4·8 ml) was added slowly to the hydrate of ulose *XVII* (400 mg) in 10 ml of ethanol and allowed to react. When the reaction ceased the mixture was allowed to stand for an additional 15 minutes and a few drops of acetic acid were added to it and the mixture evaporated. Methanol was added to the residue and evaporated. This was repeated several times. The residue was extracted with three portions of ethyl acetate, the extract filtered, evaporated, and the residue crystallized from ethyl acetate. Yield 310 mg (85%), m.p. 113–115°C, $[\alpha]_D$ –85° (*c* 0·6, chloroform). For $C_6H_8F_2O_3$ (166·1) calculated: 43·39% C, 4·86% H, 22·88% F; found: 43·71% C, 4·79% H, 22·27% F.

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

Compound *XIX* (100 mg) was allowed to stand for 24 hours with 3·5 ml of acetic anhydride containing 0·035 ml of 70% perchloric acid. Excess acetic anhydride was decomposed with water. After two hours' standing the mixture was extracted with three 15 ml portions of chloroform. The extract was washed with aqueous sodium hydrogen carbonate solution, dried, filtered with charcoal and evaporated. According to thin-layer chromatography (benzene–acetone 19 : 1) the residue contained a mixture of two substances of R_F 0·29 and 0·41, of which the product with the lower R_F value was obtained in crystalline form after column chromatography on silica gel (eluted with a mixture of benzene and acetone 19 : 1). The compound with higher R_F value is probably 3-O-acetyl-1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose. The product was recrystallized from ether, to give 44 mg (24%) of compound *XX*, m.p. 92–95°C, $[\alpha]_D$ +75° (*c* 0·6 chloroform). For $C_{12}H_{16}F_2O_7$ (310·2) calculated: 46·46% C, 5·20% H, 12·24% F; found: 46·64% C, 5·11% H, 12·34% F.

2,4-Dideoxy-2,4-difluoro-D-allopyranose (*XXI*)

Triacetate *XX* (30 mg) was dissolved in 3 ml of methanol, 2 drops of a methanolic solution of sodium methoxide were added and the mixture allowed to stand for 24 hours. Amberlite IR-120 was then added to the mixture and the neutralized solution was filtered through a small column of silica gel and charcoal. After elimination of the solvent by distillation and evacuation at 0·5 Torr the residual oil began to crystallize. The compound could not be purified. Yield 15 mg (80%), m.p. 120–130°C, $[\alpha]_D$ +15° (*c* 0·9 water). For $C_6H_{10}F_2O_4$ (184·1) calculated: 39·15% C, 5·48% H, 20·63% F; found: 40·50% C, 5·59% H, 19·83% F. This compound had R_F 0·48 on paper Whatman No 1 in 1-butanol saturated with water (detection with ammoniacal silver nitrate), which is very close to that of 2,4-dideoxy-2,4-difluoro-D-glucose[3] (0·46).

2,4-Dideoxy-2,4-difluoro-D-glucitol

A solution of 150 mg of sodium borohydride in 3·75 ml of water was added to a solution of 200 mg of 2,4-dideoxy-2,4-difluoro-D-glucose[3] in 5 ml of water. After 10 minutes Amberlite IR-120 was added until the gas development ceased. The mixture was diluted with 15 ml of water and an additional small amount of Amberlite IR-120 was added and the mixture stirred for 20 minutes. After filtration and evaporation of the filtrate the residue was dissolved four times in methanol and evaporated. The residual syrup crystallized out. After recrystallization from methanol and ethyl acetate 100 mg (49%) of the product were obtained, m.p. 100—104°C, $[\alpha]_D$ —8° (*c* 0·7, water). For $C_6H_{12}F_2O_4$ (186·0) calculated: 38·74% C, 6·50% H, 20·42% F; found: 38·42% C, 6·49% H, 20·91% F.

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-3-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XXII*)

p-Toluenesulfonyl chloride (0·75 g) was added to a cooled solution of 500 mg of compound *XVI* in 5 ml of pyridine. As the tosylation proceeded only to about 50% after 5 days (according to TLC), additional *p*-toluenesulfonyl chloride (1 g) was added to the mixture which was then heated at 35°C for 8 hours. After 10 days' standing water was added dropwise and the precipitated needles were recrystallized from chloroform. Yield 0·85 g (88%), m.p. 127°C, $[\alpha]_D$ —29° (*c* 0·7, chloroform). For $C_{13}H_{14}F_2O_5S$ (320·3) calculated: 48·74% C, 4·41% H, 11·86% F, 10·00% S; found: 49·00% C, 4·68% H, 12·07% F, 10·50% S.

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-3-O-*p*-toluenesulfonyl-β-D-allopyranose (*XXIII*)

p-Toluenesulfonyl chloride (200 mg) was added to a solution of 100 mg of *XIX* in 1 ml of pyridine and the mixture was allowed to stand for 12 hours. Water was then added to the mixture dropwise and the precipitated crystals were recrystallized from chloroform. Yield 150 mg (78%) of product, m.p. 137—138°C, $[\alpha]_D$ —63° (*c* 0·6, chloroform). For $C_{13}H_{14}F_2SO_5$ (320·3) calculated: 48·74% C, 4·41% H, 11·86% F, 10·00% S; found 48·84% C, 4·52% H, 12·10% F, 10·13% S.

The authors are indebted to Dr M. Budešínský, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, for the measurement and the interpretation of the ^{1}H-NMR *spectra and to Dr J. Horáček of the same institute for fluorine analyses.*

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Translated by Ž. Procházka.