SYNTHESES WITH ANHYDRO SUGARS. XIV.*

SYNTHESIS OF SOME DERIVATIVES OF 1,6-ANHYDRO-4-DEOXY-4-FLUORO-β-D-GLUCOPYRANOSE

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Reaction of 1,6 : 3,4-dianhydro-2-O-benzyl-β-D-galactopyranose (*IV*) with potassium hydrogen fluoride in boiling ethylene glycol gave 4-deoxy-4-fluoro derivative *VII*, which on catalytic debenzylation and partial tosylation afforded 1,6-anhydro-4-deoxy-4-fluoro-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*II*). This compound is also formed in a low yield during the reaction of 1,6 : 3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose (*I*) with anhydrous hydrogen fluoride in dioxane. Cleavage of 1,6 : 2,3-dianhydro-4-O-*p*-toluenesulfonyl-β-D-mannopyranose (*V*) with potassium hydrogen fluoride in boiling ethylene glycol gave 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*III*) in a better yield than when it was prepared by the same method from *I*.

One of us[1] has described the cleavage of 1,6:3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose[2] (*I*) with hydrogen fluoride in dioxane at 120°C; after the isolation, by silica gel chromatography of the reaction mixture, a crystalline compound was obtained in a very low yield, the elemental analysis of which corresponded to 1,6-anhydro-4-deoxy-4-fluoro-2-O-p-toluenesulfonyl-β-D-glucopyranose (*II*). In order to confirm the structure of the mentioned compound we decided to prepare it by another unambiguous route[3,4]. In the meanwhile compound *II* has been described by Barford and coworkers[5] in connection with the preparation of 4-deoxy-4-fluoro-D-glucose. In addition to other proofs its structure was proved by transforming it to 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (*III*) described earlier[6,7], *via* 1,6:2,3-dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (*IX*) as an intermediate.

In contrast to Barford and coworkers we did not start our synthesis of compound II with 1,6:3,4-dianhydro-β-D-galactopyranose (*XVIII*), but with its 2-O-benzyl ether *IV* which we prepared both by detosylation of *I* with sodium amalgam[8] and subsequent benzylation[9], and by acid catalysed cleavage of 1,6:2,3-dianhydro-4-O-*p*-toluenesulfonyl-β-D-mannopyranose[10] (*V*) with benzyl alcohol; the formed 1,6-

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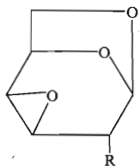
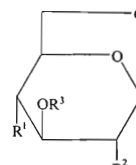
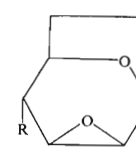
anhydro-2-O-benzyl-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VI*) was transformed to compound *IV* under the effect of alkoxide. The first preparation was found more convenient.



I, R = OTs
IV, R = OBz
XIV, R = F
XVIII, R = OH



II; R^1 = F, R^2 = OTs, R^3 = H
III; R^1 = R^2 = F, R^3 = H
VI; R^1 = OTs, R^2 = OBz, R^3 = H
VII; R^1 = F, R^2 = OBz, R^3 = H
VIII; R^1 = F, R^2 = OH, R^3 = H
X, R^1 = F, R^2 = OBz, R^3 = Ac
XI; R^1 = F, R^2 = OH, R^3 = Ac
XII; R^1 = F, R^2 = OTs, R^3 = Ac
XIII; R^1 = OTs, R^2 = F, R^3 = H
XVI; R^1 = R^2 = OBz, R^3 = H
XVII; R^1 = OBz, R^2 = OTs, R^3 = H



V, R = OTs
IX, R = F
XV, R = OBz

Ts = *p*-toluenesulfonyl; Bz = benzyl; Ac = acetyl.

The epoxide ring of compound *IV* is cleaved under the effect of potassium hydrogen fluoride in boiling ethylene glycol, affording 1,6-anhydro-2-O-benzyl-4-deoxy-4-fluoro-β-D-glucopyranose (*VII*), as required by the Fürst-Plattner rule. The presence of the benzyl group in this compound greatly facilitates its isolation from the reaction mixture. Catalytic debenzylation on palladium on charcoal of compound *VII* gives rise to 1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose[5] (*VIII*) which on partial tosylation affords compound *II*. The latter compound is identical with a product obtained on reaction of *I* with hydrogen fluoride in dioxane, and in its properties it corresponds to the compound prepared by Barford and coworkers[5] in the same manner. Reaction of *II* with sodium ethoxide leads to 1,6:2,3-dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (*IX*) the rotation of which differs slightly from the value given by the above mentioned authors. The yields of epoxide can be substantially increased if instead of *VII* its 3-O-acetyl derivative *X* is used for the preparation, with which the following reaction sequence is then carried out: *X* → *XI* → *XII* → *IX*. The attempts at the preparation of compound *II* or its acetate *XII* by cleavage of compound *I* with a mixture of hydrogen fluoride and acetic anhydride (1 : 1) at temperatures between −70°C and 0°C were unsuccessful.

It has been described earlier[6,7] that compound *I* was transformed to *III* under the effect of potassium hydrogen fluoride in boiling ethylene glycol. We therefore allowed its isomer *V* to react under the same conditions. The transformation $V \rightarrow III$ takes place in a higher yield than $I \rightarrow III$. We suppose that in this reaction compound *V* is transformed first to 1,6-anhydro-2-deoxy-2-fluoro-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XIII*) which is then changed to an alkoxide ion under the effect of fluoride ions liberated after the splitting off of hydrogen fluoride from potassium hydrogen fluoride. The alkoxide ion is then cyclised to 1,6 : 3,4-dianhydro-2-deoxy-2-fluoro-β-D-galactopyranose (*XIV*). The latter is then transformed to derivative *III* under the effect of excess potassium hydrogen fluoride. The presence of one of the supposed intermediates, *XIII*, could be proved in the chloroform extract of the reaction mixture by gas chromatography after its transformation to epoxide *XIV*.

In connection with the preparation of compound *IV* we found that the cleavage of the oxiran ring of 1,6:2,3-dianhydro-4-O-*p*-toluenesulfonyl-β-D-mannopyranose (*V*) with benzyl alcohol, catalysed with *p*-toluenesulfonic acid, during which 1,6-anhydro-2-O-benzyl-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VI*) is formed, takes place with greater difficulty than the analogous cleavage of 1,6:3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose (*I*) to 1,6-anhydro-4-O-benzyl-2-O-*p*-toluenesulfonyl-β-D-glucopyranose[11] (*XVII*). This is in agreement with the behaviour of isomeric compounds *IV* and *XV* (ref.[12]) toward the same reagents, when *XV* affords 1,6-anhydro-2,4-di-O-benzyl-β-D-glucopyranose[13] (*XVI*) less easily than compound *IV* does.

EXPERIMENTAL

Melting points were measured on a micromelting point apparatus Boetius, optical rotations on an automatic polarimeter Bendix Ericsson, type 143 A. Samples for analysis were dried at 1 Torr pressure over P_2O_5. The solvents used were distilled on a vacuum rotatory evaporator at 20—100°C temperatures. Thin-layer chromatography was carried out on Kieselgel G Stahl, granulation 10—40 μ, content of calcium sulfate 13% (Merck). R_F values are given for benzene–acetone (4 : 1) solvent system. Detection of thin-layer chromatograms was carried out by carbonisation (heating) after spraying with 50% H_2SO_4. Gas chromatography was carried out on Chrom III IKZ (Laboratory apparatus, Prague). Solutions were dried over anhydrous magnesium sulfate.

1,6-Anhydro-2-O-benzyl-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VI*)

A solution of 10 g of *V* (ref.[10]) in 60 ml of benzene was mixed with 16 ml of benzyl alcohol and 1·2 g of *p*-toluenesulfonic acid. The mixture was refluxed for 40 h and the reaction course controlled by chromatography. When all compound *V* was reacted 50 ml of chloroform were added and the solution washed with three 50 ml portions of water. The organic phase was then dried, filtered with charcoal and evaporated. After the addition of ether to the residue at −5°C it crystallised out. After double crystallisation from ethanol and an additional crystallisation from benzene 4·15 g (32%) of product were obtained, the m.p. of which was 104—106°C, $[\alpha]_D$ −50° (0·7; chloroform), and R_F 0·49. For $C_{20}H_{22}O_7S$ (406·5) calculated: 59·10% C, 5·40% H, 7·89% S; found: 59·14% C, 5·66% H, 7·83% S. For an analogous cleavage of the isomeric epoxide *I* only a two-hours heating was necessary[11].

1,6 : 3,4-Dianhydro-2-O-benzyl-β-D-galactopyranose (*IV*)

A solution of compound *VI* (2 g) in 25 ml of chloroform was mixed with a solution of Na (1 g) in 10 ml of methanol and the mixture was allowed to stand for 12 h. It was then poured into 150 ml of water and the chloroform layer was separated. The aqueous phase was extracted three times with 50 ml portions of chloroform and the chloroform extracts were combined, dried, filtered with charcoal, and evaporated. The residual oil (1·15 g; 85%) had R_F 0·81 and it was identical with a product prepared on benzylation of 1,6 : 3,4-dianhydro-β-D-galactopyranose[9].

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

A mixture of 20 g of compound *IV*, 27 g of potassium hydrogen fluoride, and 250 ml of ethylene glycol was heated at 225°C (bath temperature) for 4 h. After cooling the mixture was poured into 1000 ml of 10% aqueous potassium carbonate, extracted with five 100 ml portions of chloroform, which were pooled, then washed with water, dried, and evaporated. The residue was dissolved in ether, the solution washed three times with 75 ml of water, dried, and evaporated to dryness. The residue (17·6 g) was chromatographed on 500 g of silica gel (70—140 μ) with benzene–acetone (9 : 1). The fractions the R_F values of which on thin-layer chromatography in benzene–acetone (4 : 1) were 0·58 were combined and evaporated. The obtained syrup (12 g; 55%) was crystallised from ether–light petroleum to afford 9 g of product, m.p. 65—69°C, $[\alpha]_D$ −47° (0·7; chloroform). For $C_{13}H_{15}FO_4$ (254·3) calculated: 61·40% C, 5·95% H, 7·47% F; found: 61·20% C, 5·78% H, 7·32% F.

1,6-Anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (*VIII*)

To a solution of 600 mg of compound *VII* in 30 ml of ethanol 150 mg of 10% palladised charcoal were added and the mixture was hydrogenolysed at 40°C until the hydrogen consumption ceased (approx. 4 h). After filtration, evaporation, and crystallisation from an ethanol–acetone–ether mixture 355 mg (92%) of a compound of m.p. 116·5—119°C, $[\alpha]_D$ −48° (0·7; water), and R_F 0·14 were obtained. These values are consistent with those from the literature[5].

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

A mixture of 4 g of epoxide *I* (ref.[2]), 50 ml of dioxane, and 50 ml of a 50% anhydrous hydrogen fluoride solution in dioxane was heated in an autoclave of Monel alloy with a teflon packing at 120—125°C for 10 h. The mixture was concetrated in a teflon crucible to an oil which was dissolved in 100 ml of chloroform; the solution was washed with seven 50 ml portions of water, once with 50 ml of a saturated sodium hydrogen carbonate solution, and again three times with 50 ml of water. After drying and filtration with charcoal chloroform was evaporated and the residue, containing unreacted epoxide *I*, was dissolved in ethanol from which it crystallised out upon standing. After filtration and evaporation of ethanol the residue was chromatographed on a silica gel column (300 g; 50—90 μ; benzene–acetone 9 : 1), to afford 85 mg (2%) of a residue the R_F value of which was 0·55. After crystallisation from benzene the substance had m.p. 115 to 116°C, $[\alpha]_D$ −48° (1·0; chloroform). The product obtained in this manner was identical with that prepared by partial tosylation[5] of *VIII*.

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

A mixture of 3 g of compound *VII*, 3 g of anhydrous sodium acetate, and 37·5 ml of acetic anhydride was refluxed for 15 minutes and then poured into 400 ml of water. After 20 h standing

(occasional shaking) the mixture was extracted with chloroform (five 50 ml portions) and the combined extracts were washed twice with 100 ml of an aqueous $NaHCO_3$ solution and twice with 100 ml of water. After drying, treatment with charcoal, and filtration the solution was evaporated and the residual syrup dissolved in ether and diluted with light petroleum for crystallisation. The product was recrystallised from a mixture of the same solvents to afford 2·8 g (80%), m.p. 47·5—49°C, $[\alpha]_D$ —129° (0·7; chloroform), R_F 0·75. For $C_{15}H_{17}FO_5$ (296·3) calculated: 60·80% C, 5·78% H, 6·41% F; found: 60·31% C, 5·75% H, 6·58% F.

3-O-Acetyl-1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (*XI*)

A solution of 2 g of compound *X* in 30 ml of ethanol was additioned withd 600 mg of 10% palladised charcoal and hydrogenated at 40°C for approximately 6 h. After elimination of the catalyst by filtration the filtrate was treated with charcoal, filtered and evaporated; the residue, m.p. 55—65°C, was crystallised from ether–light petroleum. Yield 1·9 g (97·5%), m.p. 102—104°C, $[\alpha]_D$ —78° (0·6; chloroform), R_F 0·38. For $C_8H_{11}FO_5$ (206·1) calculated: 46·60% C, 5·38% H, 9·22% F; found: 46·45% C, 5·70% H, 9·35% F.

3-O-Acetyl-1,6-anhydro-4-deoxy-4-fluoro-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*XII*)

A solution of 1·9 g of compound *XI* and 2 g of *p*-toluenesulfonyl chloride in 15 ml of pyridine was allowed to stand for 50 h and then poured into water and extracted with five 70 ml portions of chloroform. The combined extracts were washed three times with 50 ml of 5% aqueous HCl and twice with 50 ml of water. After drying and filtration with charcoal the solvent was evaporated and the residue crystallised from ethanol–acetone–light petroleum mixture. Yield 2·3 g (70·6%) of product, m.p. 130·5—132°C, $[\alpha]_D$ —26° (0·6; chloroform). For $C_{15}H_{17}FO_7S$ (360·4) calculated: 49·99% C, 4·76% H, 5·27% F, 8·90% S; found: 50·21% C, 5·09% H, 5·49% F, 8·91% S.

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

To a solution of 2·5 g of compound *XII* in a minimum amount of chloroform sodium (0·4 g) dissolved in 8 ml of methanol was added under stirring which was continued for another 4 h at room temperature. The mixture was poured into 350 ml of water and the solution extracted, with 8 × 50 ml of chloroform. The combined extracts were washed with 100 ml of water, dried, filtered with charcoal, and evaporated. Crystallisation from a mixture of ether and light petroleum gave 0·85 g (85%) of product, m.p. 45—46°C, $[\alpha]_D$ —53° (0·6; chloroform), R_F 0·76, identical with the product obtained from tosyl derivative *II* under the effect of sodium methoxide[5]. The identity of both samples was proved by their mixed melting point and identical behaviour on gas chromatography (column 183 cm, 5 mm diameter, filled with 3·5% OV 101 on Chromosorb W-AW-sil., 110°C, nitrogen flow 24 ml/min, overpressure on column 1·9 kp/cm^2).

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

A mixture of 6·75 g of compound *V*, 25 g of KHF_2 and 600 ml of ethylene glycol was refluxed for 4 h, then poured into 1 500 ml of a saturated aqueous $NaHCO_3$ solution and extracted with five 100 ml portions of chloroform and ten 100 ml portions of ether. The combined ethereal extracts were dried and evaporated. The residue gave after crystallisation 500 mg (15%) of a compound, m.p. 97—100°C, which melted undepressed on admixture of the authentic[6,7] sample *III*. Their IR spectra, retention times on gas chfomatography, and R_F values were also identical. In the chloroform extract the presence of 1,6-anhydro-2-deoxy-2-fluoro-4-O-*p*-toluenesulfonyl-β-D-glucopyranose

(*XIII*) was proved, representing an intermediate in the synthesis of *III* from *V*; the proof was carried out by gas chromatography after transformation of *XIII* to epoxide *XIV* under the effect of sodium methoxide (glass column 183 cm long, 5 mm diameter, filling 3·5% OV 101 on Chromosorb W-AW-sil., 141°C, overpressure 2·1 kp/cm^2, nitrogen flow 23 ml/min). Its retention time is identical with that of the epoxide sample prepared by a different method[6,7]. The epoxide *XIV* could not be proved in the chloroform extract before the reaction with methoxide.

1,6-Anhydro-2,4-di-O-benzyl-β-D-glucopyranose (*XVI*)

A mixture of 1 g of compound[12] *XV*, 20 ml of benzene, 50 mg of *p*-toluenesulfonic acid, and 1 ml of benzyl alcohol was refluxed for 32 h. Every 8 h 0·5 ml of benzyl alcohol and 10 mg of *p*-toluenesulfonic acid were added. When, according to chromatographic analysis, the mixture did not contain any starting material, it was evaporated, the residue dissolved in chloroform, and the solution washed with water, dried, filtered with charcoal, and evaporated. The residue was crystallised from ethanol. Yield 450 mg (36%), m. p. 102—104°C, R_F 0·62. The melting point coincides with the literature data[13]. From 1 g of compound[9] *IV* 400 mg (32%) of the same dibenzyl derivative *XVI* were obtained by an analogous procedure after 24 h.

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