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FLUOROCARBOHYDRATES

PART XVI. THE SYNTHESIS OF 3-DEOXY-3-FLUORO-D-XYLOSE AND 3-DEOXY-3-FLUORO-β-D-ARABINOSE*

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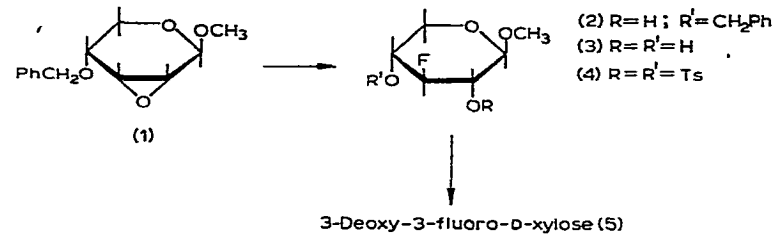
INTRODUCTION

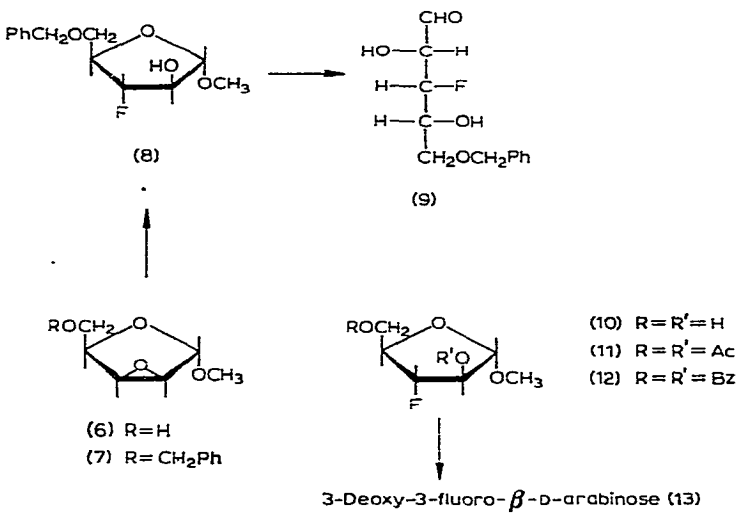
Since our preliminary communication[1] the synthesis of a number of secondary fluorosugars has been reported. Thus, Codington, Doerr, and Fox[2] have synthesised 2-deoxy-2-fluoro-D-ribose from 2′-deoxy-2′-fluorouridine and another group[3] has reported the synthesis of 2-deoxy-2-fluoro-D-allose, 2-deoxy-2-fluoro-D-altrose, and 3-deoxy-3-fluoro-D-glucose by the action of hydrogen tetrafluoridoborate in hydrogen fluoride on suitably blocked 2,3-anhydro-D-allosides. We now report on a synthesis of 3-deoxy-3-fluoro-D-xylose and 3-deoxy-3-fluoro-β-D-arabinose.

RESULTS AND DISCUSSION

The successful scission of aliphatic epoxides[4] and steroid epoxides[5,6] by hydrogen fluoride has been know for some time and originally, as a model for such studies in the carbohydrate series, we examined the action of anhydrous hydrogen fluoride in dioxan on methyl 2,3-anhydro-4-*O*-benzyl-β-L-ribopyranoside[1]. While this work was in progress Cohen, Levy, and Bergmann[7] reported the use of potassium hydrogen fluoride (KHF_2) in ethane-1,2-diol for the scission of benzyl 2,3-anhydro-β-D-ribopyranoside to give benzyl 3-deoxy-3-fluoro-β-D-xylopyranoside which, on catalytic hydrogenation, gave 3-deoxy-3-fluoro-D-xylose. We have now examined the action of potassium hydrogen fluoride in ethanediol on methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside (**1**), (also in the L series) and found that much improved and less contaminated yields of the fluorohydrin (**2**) are obtained by this procedure than those obtained by the action of hydrogen fluoride in dioxan on compound (**1**). The structure of compound (**2**) was established by catalytic hydrogenation (palladium on charcoal) which removed the benzyl group to give the glycoside (**3**) as a crystalline material which did not reduce Fehling's solution or consume periodate and contained fluorine[8]. The retention of the fluorine under these conditions was expected as a result of previous work with 6-deoxy-6-fluoro-D-galactose[9]. Thin-layer chromatography[10] (t.l.c.) of compound (**3**) gave only one component (R_F, 0.4, ethyl acetate) and paper chromatography followed by treatment with periodate and benzidine did not reveal the presence of vicinal hydroxyl groups[11]. The glycoside (**3**) was further characterised as the di-*O*-

toluene-*p*-sulphonyl derivative (**4**). These results are in accordance with the expected *trans* scission[12] of the epoxide (**1**) and so the structure methyl 3-deoxy-3-fluoro-β-D-xylopyranoside was assigned to compound (**3**). Acid hydrolysis of compound (**3**) with 0.05M sulphuric acid gave rise to a reducing sugar as a syrup which was characterised as the 2,5-dichlorophenylhydrazone and assigned the structure 3-deoxy-3-fluoro-αβ-D-xylose (**5**).





In order to examine the general applicability of this method of introducing fluorine into carbohydrates we have also examined the action of potassium hydrogen fluoride in ethane-1,2-diol on methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside (**7**) obtained in good yields by the benzylation of methyl 2,3-anhydro-α-D-lyxofuranoside[13] (**6**). Refluxing compound (**7**) with potassium hydrogen fluoride in ethane-1,2-diol for 1 h gave a product which was shown by t.l.c. to contain two major components (R_F, 0.5 and 0.6, ethyl acetate–light petroleum, 1:1) one of which was shown to be starting material (R_F, 0.6) and the other a fluorohydrin. The latter compound was isolated by preparative t.l.c. as a syrup which gave the correct elemental analysis and showed characteristic bands at 3500 (OH) and 1040 cm^{-1} (C–F) in the infrared spectrum. The structure of the fluorohydrin (**8**) was established by hydrolysis with 0.125M sulphuric

acid to give a reducing sugar (R_F, 0.37, ethyl acetate–light petroleum, 1:1) which did not crystallise but readily formed a crystalline phenylhydrazone derivative. The reducing sugar (**9**) was shown to consume 1 mol. of periodate[14] with the liberation of 0.7 mol. of formic acid[15]. Such a result is consistent with the structure of 5-*O*-benzyl-3-deoxy-3-fluoro-$\alpha\beta$-D-arabinose if we assume *trans* opening[12] of the epoxide ring in (**7**). On this basis, the structure methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside was assigned to the fluorohydrin (**8**). Catalytic hydrogenation of compound (**8**) with 5% palladium on charcoal removed the benzyl group to give a non-reducing glycoside (**10**) as a syrup (R_F, 0.2, ethyl acetate–light petroleum, 1:1) containing fluorine and characterised as the non-crystalline 2,5-diacetate (**11**) and the crystalline 2,5-dibenzoate (**12**). Acid hydrolysis of compound (**10**) with 0.1N sulphuric acid gave a reducing syrup (R_F, 0.15, ethyl acetate) which failed to crystallise spontaneously but immediately crystallised on seeding with a crystal of β-D-arabinose. On the basis of the mutarotation of the free sugar (**13**) ($[\alpha]_D^{20}$ $-150° \rightarrow -105°$, water) it was assigned the structure 3-deoxy-3-fluoro-β-D-arabinose and further characterised as the crystalline 2,5-dichlorophenylhydrazone.

The biological activity of 3-deoxy-3-fluoro-D-arabinose and 3-deoxy-3-fluoro-D-xylose is now being investigated in these laboratories.

EXPERIMENTAL

Melting points were determined by an Electrothermal apparatus and are uncorrected. Paper chromatography was carried out on Whatman No. 1 paper using the organic phase of butanol–ethanol–water (4:1:5). Reducing sugars were detected with aniline hydrogen phthalate[16] and glycosides were detected with a 1% solution of sodium metaperiodate in acetone followed by benzidine[11]. Column chromatography was carried out with aluminium oxide for chromatographic absorption (British Drug Houses Ltd.). T.l.c. plates (40 × 20 cm) were prepared with Silica-gel G, according to Stahl (Shandon Scientific Co. Ltd.). After the solvent was removed from the developed plate it was sprayed with sulphuric acid–ethanol (1:1) and heated to 100° for ten min. All preparative t.l.c. plates (20 × 20 cm) were prepared with Silica-gel PF 254 (Shandon Scientific Co. Ltd.). After the solvent had been removed from the developed plate it was examined under ultraviolet light (254 mμ) and the different zones eluted.

The solvent systems used were light petroleum (b.p. 40–60°)–ethyl acetate, 4:1 (*A*), 1:1 (*B*) and ethyl acetate (*C*).

Microanalyses and fluorine determinations were carried out by Drs. Weiler and Strauss, Oxford.

Methyl 4-O-benzyl-3-deoxy-3-fluoro-β-D-xylopyranoside (**2**). — Methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside[18] (**1**) (2.0 g) in ethane-1,2-diol (40 ml) containing potassium hydrogen fluoride (4.0 g) was refluxed gently for 40 min. On cooling, the mixture was poured, with stirring, into a cold, saturated solution of sodium hydrogen carbonate. The neutral solution was extracted with ether (3 × 75 ml), dried (Na_2SO_4), and evaporated to dryness. T.l.c. (solvent *B*) of the resulting syrup,

revealed two major components R_F, 0.5 and 0.65. The syrup was submitted to column chromatography and eluted with ether to yield starting material (0.6 g) (t.l.c. R_F, 0.65, solvent *B*). Elution with chloroform yielded a product (1.0 g) which crystallised on storage at room temperature and was recrystallised from ether–light petroleum (b.p. 40–60°) to give the title compound as large needles, m.p. 84°, $[\alpha]_D^{20}$ −50.5° (*c* 1.35, chloroform) (Found: C, 61.0; H, 6.6; F, 7.4. $C_{13}H_{17}FO_4$ calc.: C, 60.9; H, 6.6; F, 7.2%).

*Methyl 3-deoxy-3-fluoro-β-*D*-xylopyranoside* (**3**).—Methyl 4-*O*-benzyl-3-deoxy-3-fluoro-β-D-xylopyranoside (**2**) (1.0 g) in ethanol (20 ml) containing 5% palladium on charcoal (500 mg) was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased (2 h). The mixture was filtered and evaporated to dryness *in vacuo* to leave a syrup which crystallised on storage. Recrystallisation from methanol–ether gave the product, m.p. 105° (Found: C 44.0; H, 6.7; F, 11.1. $C_6H_{11}FO_4$ calc.: C, 43.4; H, 6.6; F, 11.4%).

The glycoside did not reduce Fehling's solution or consume periodate. Paper chromatography and detection with periodate–benzidine[11] did not reveal the presence of vicinal hydroxy groups thus indicating the 3-deoxy-3-fluoroxylose configuration for for the glycoside. The glycoside was further characterised as the 2,4-ditoluene-*p*-sulphonate (**4**), needles, m.p. 138°, $[\alpha]_D^{20}$ −35° (*c* 0.57, chloroform) (Found: C, 50.9; H, 4.7; S, 13.7; F, 4.0. $C_{20}H_{23}FO_8S_2$ calc.: C, 50.6; H, 4.9; S, 13.5; F, 4.0%).

*3-Deoxy-3-fluoro-αβ-*D*-xylose* (**5**). — Methyl 3-deoxy-3-fluoro-β-D-xylopyranoside (**3**) (1.0 g) was refluxed with 0.05M sulphuric acid (100 ml) for 1 h, allowed to cool, and neutralised with barium carbonate. After filtration, the solution was evaporated to dryness *in vacuo*, the residue was dissolved in ethanol and the filtered solution evaporated to dryness *in vacuo*. A portion (28.5 mg) of the resulting viscous syrup (R_F , 0.24, t.l.c. solvent *C*) was treated with 2,5-dichlorophenylhydrazine (92.5 mg) in methanol (15 ml). The methanol was evaporated and the residue was crystallised from aqueous methanol by allowing to stand in the refrigerator overnight. Recrystallisation from aqueous methanol gave the 2,5-dichlorophenylhydrazone, m.p. 75° (Found: C, 43.0; H, 4.6; N, 9.9; F, 6.5. $C_{11}H_{13}Cl_2FN_2O_3$ calc.: C, 42.5; H, 4.46; N, 9.6; F, 6.48%).

*Methyl 2,3-anhydro-5-*O*-benzyl-α-*D*-lyxofuranoside* (**7**).—To methyl 2,3-anhydro-α-D-lyxofuranoside[13] (**6**) (5.0 g) in anhydrous dimethylformamide (25 ml) were added silver oxide (7.0 g) and benzyl bromide (6 ml). The mixture was shaken for 24 h at room temperature then diluted with chloroform (250 ml) and water (250 ml). The chloroform layer was separated and filtered, pyridine (30 ml) was added, and the solution washed successively with water (6 × 100 ml), 2M hydrochloric acid (3 × 100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), and water (100 ml). The chloroform extract was dried ($MgSO_4$), evaporated to dryness, and the resulting light brown oil distilled to give the product as a colourless oil (6.5 g), n_D^{20} 1.5192, b.p. 135° (bath)/0.01 mm, $[\alpha]_D^{20}$ +23.4° (*c* 5.8, chloroform) (Found: C, 66.3; H, 6.65. $C_{13}H_{16}O_4$ calc.: C, 66.1; H, 6.7%).

*Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-*D*-arabinofuranoside* (**8**). — Methyl 2,3-

anhydro-5-*O*-benzyl-α-D-lyxofuranoside (**7**) (3.0 g) and potassium hydrogen fluoride (6.0 g) in ethane-1,2-diol (60.0 ml) were refluxed gently for 1 h. When cool, the solution was poured into saturated aqueous sodium hydrogen carbonate (500 ml) with stirring and extracted with chloroform (3 × 100 ml) and the extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The resulting syrup on t.l.c. (solvent *B*) was found to contain two major components, R_F, 0.5 and 0.6, one of which was shown to be starting material (R_F, 0.6 and comparative i.r. spectrum). The mixture was submitted to preparative t.l.c. using two elutions with solvent *A* to yield a fluorine-containing syrup (0.9 g), $[\alpha]_D^{20}$ +87° (*c* 0.9, chloroform) with i.r. bands at 3500 (OH) and 1050 cm^{-1} (C–F) (Found: C, 61.2; H, 6.6; F, 7.4. $C_{13}H_{17}FO_4$ calc.: C, 61.0; H, 6.6; F, 7.2%).

5-O-Benzyl-3-deoxy-3-fluoro-αβ-D-arabinose (**9**). — Methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (**8**) (1.0 g) was dissolved in a mixture of dioxan (50.0 ml) and 0.25M sulphuric acid (50.0 ml) and the solution was refluxed for 3 h. The cold solution was neutralised with barium carbonate, filtered, and evaporated to dryness *in vacuo*. The residue was taken up in absolute ethanol (50.0 ml), filtered, and the filtrate evaporated to dryness *in vacuo* to yield a viscous colourless syrup (890 mg), R_F, 0.37 (t.l.c. solvent B), $[\alpha]_D^{20}$ +107° (*c* 1.4, ethanol) (Found: C, 59.9; H, 6.6; F, 7.4. $C_{12}H_{15}FO_4$ calc.: C, 59.5; H, 6.2; F, 7.8%). The free sugar (250 mg) in water (2.5 ml) was treated with a solution of phenylhydrazine hydrochloride (175 mg) and sodium acetate (175 mg) in water (5.0 ml). A yellow oil separated which solidified on cooling. Recrystallisation from aqueous ethanol gave the phenylhydrazone, m.p. 72° (Found: C, 64.9; H, 6.3; N, 8.7; F, 6.0. $C_{18}H_{21}FN_2O_3$ calc.: C, 65.0; H, 6.3; N, 8.5; F, 5.7%).

Periodate oxidation of 5-O-benzyl-3-deoxy-3-fluoro-αβ-D-arabinose (**9**). — 5-*O*-Benzyl-3-deoxy-3-fluoro-αβ-D-arabinose (**9**) (42.8 mg) was dissolved in water (10.0 ml) and 0.05M sodium metaperiodate (10 ml). At intervals, 2 ml portions were added to 0.025M sodium arsenite (5 ml) and 20% aqueous potassium iodide (1 ml). Excess arsenite was titrated against standard iodine to the starch end-point. The periodate consumed was as follows:

Time (min)	5	10	15	30	24 (h)
$NaIO_4$ consumed (mol.)	0.77	0.87	0.9	0.92	1.00

5-*O*-Benzyl-3-deoxy-3-fluoro-αβ-D-arabinose (**9**) (50.3 mg) was dissolved in water (10.0 ml) and 0.05M sodium metaperiodate (10 ml). At intervals, 2 ml portions were removed and excess periodate was destroyed by the addition of ethane-1,2-diol (1.0 ml) The acid was determined[15] using 0.01M sodium hydroxide, and phenolphthalein–thymol blue (3:1) as an indicator. The results were as follows:

Time (h)	0.25	0.5	1.0	4.0	8.0
Acid liberated (mol.) .	0.60	0.62	0.65	0.73	0.73

The acid liberated was identified as formic acid by reduction to formaldehyde and characterisation with chromotropic acid[17].

Methyl 3-Deoxy-3-fluoro-α-D-arabinoside (**10**). — Methyl 5-*O*-benzyl-3-deoxy-3-

fluoro-α-D-arabinofuranoside (**8**) (1.0 g) in ethanol (25.0 ml) containing 5% palladium on charcaol (1.0 g) was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased (3 h). After filtration, the solution was evaporated to dryness *in vacuo* to leave a viscous non-reducing syrup (**10**), R_F, 0.19 (t.l.c., solvent *B*), $[\alpha]_D^{20}+107°$ (*c* 1.0, ethanol) (Found: C, 43.2; H, 6.8; F, 11.2. $C_6H_{11}FO_4$: calc.: C, 43.4; H, 6.6; F, 11.4 %). The glycoside (**10**) was further characterised as the non-crystalline 2,5-diacetate (**11**) (Found: C, 48.4; H, 6.2; F, 7.6; $C_{10}H_{15}FO_6$: calc.: C, 48.0; H, 6.0; F, 7.6%) and the 2,5-dibenzoate (**12**) m.p. 81° (Found: C, 64.1; H, 5.3; F, 5.5. $C_{20}H_{19}FO_6$ calc.: C, 64.1; H, 5.1; F, 5.1%).

3-Deoxy-3-fluoro-β-D-arabinose (**13**). — Methyl 3-deoxy-3-fluoro-α-D-arabinofuranoside (**10**) (1.0 g) in 0.1N sulphuric acid (100 ml) was refluxed for 1 h then allowed to cool and neutralised with barium carbonate. The filtered solution was evaporated to dryness *in vacuo*, the residue was taken up in absolute ethanol, and the solution filtered and evaporated to dryness *in vacuo* to leave a viscous syrup (850 mg), R_F, 0.15 (t.l.c., solvent *C*). On addition of a crystal of β-D-arabinose the syrup crystallised. Recrystallisation from ethanol gave the title compound as colourless plates, m.p. 120°, $[\alpha]_D^{20}$ $-150° \rightarrow 105°$ (*c* 1.0 water), (Found: C, 39.7; H, 6.1; F, 12.8. $C_5H_9FO_4$ calc.: C, 39.5; H, 5.9; *F*, 12.5%). To the fluorosugar (100 mg) in methanol (3.0 ml), 2,5-dichlorophenylhydrazine (130 mg) was added and the solution was evaporated to dryness. Trituration of the residue with ether–light petroleum (b.p. 40–60°) and recrystallisation from the same solvent system gave the 2,5-dichlorophenylhydrazone, m.p. 120°, (Found: C, 42.8; H, 4.3; N, 9.3; F, 5.9. $C_{11}H_{13}Cl_2FN_2O_3$ calc.: C, 42.5; H, 4.2; N, 9.6; F, 6.1 %).

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SUMMARY

The action of potassium hydrogen fluoride (KHF_2) in ethane-1,2-diol on methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside (**1**) and methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside (**7**) has been examined. In both cases the expected *trans* scission of the epoxide ring occurs to yield methyl 4-*O*-benzyl-3-deoxy-3-fluoro-β-D-xylopyranoside (**2**) and methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (**8**) respectively. The structure of compound (**2**) was established by catalytic hydrogenation, which removed the benzyl group, to yield a crystalline glycoside (**3**) which did not consume periodate. Acid hydrolysis of methyl 3-deoxy-3-fluoro-β-D-xylopyranoside (**3**) yielded syrupy 3-deoxy-3-fluoro-αβ-D-xylose (**5**) characterised as the 2,5-dichlorophenylhydrazone.

Acid hydrolysis of compound (**8**) yielded a reducing sugar (**9**) characterised as the phenylhydrazone. Compound (**9**) consumed 1 mol. of periodate and liberated formic

acid which is consistent with the structure 5-*O*-benzyl-3-deoxy-3-fluoro-α,β-D-arabinose. Catalytic hydrogenation of the fluorohydrin (**8**) removed the benzyl group to give methyl 3-deoxy-3-fluoro-α-D-arabinofuranoside (**10**) which, on acid hydrolysis, yielded crystalline 3-deoxy-3-fluoro-β-D-arabinose (**13**). The β configuration was assigned to compound (**13**) on the basis of its mutarotation.

This method of introducing fluorine into carbohydrates affords reasonable yields of uncontaminated fluorohydrins and is considered to have general applicability.

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