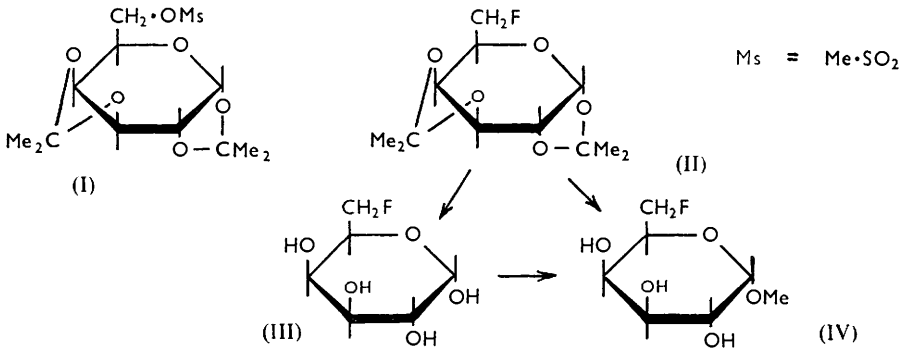
168. *Fluorocarbohydrates. Part I. The Synthesis of 6-Deoxy-6-fluoro-α-D-galactose and 5-Deoxy-5-fluoro-αβ-D-ribose.*

By N. F. Taylor and P. W. Kent.

Fluorinated monosaccharides have been synthesised by exchange reactions in ethanediol with anhydrous potassium fluoride and the appropriate primary methanesulphonyl esters. In methanol, halogenation is accompanied by the introduction of one *O*-methyl group into the product. The described deoxy-fluoro-sugars appear to behave normally towards sodium metaperiodate and are converted into the glycosides by methanolic hydrogen chloride.

The similarity in size and electronegativity of the fluorine atom and the hydroxyl group, coupled with their capacity to enter into hydrogen-bond formation, suggests the possibility of a new class of carbohydrates in which one or more of the hydroxyl groups have been replaced by fluorine. In 1941 Helferich and Gnüchtel [1] synthesised 6-deoxy-6-fluoro-α-D-glucopyranose by an exchange reaction between hydrated potassium fluoride and 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranose. Two other routes have been reported for the introduction of fluorine into carbohydrates: (*a*) the action of anhydrous hydrogen fluoride on fully acetylated sugars, to give glucosyl fluorides; [2] and (*b*) total synthesis, as in the case of 2-deoxy-2-fluoro-DL-glyceraldehyde.[3]

We have now investigated the action of potassium fluoride on the sulphonyloxy-derivatives of D-galactose and D-ribose with the object of establishing a general method for the introduction of fluorine into extracyclic positions of carbohydrate molecules.



In contrast to 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucose, attempts to replace the methanesulphonyloxy-group by fluorine in 6-*O*-methanesulphonyl-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactose (I) under Helferich and Gnüchtel's conditions (100° for 15 hr. in methanol) were unsuccessful. Exchange occurred however at 150°. A similar difference in reactivity of these two methanesulphonyl compounds towards iodide exchange is known.[4]

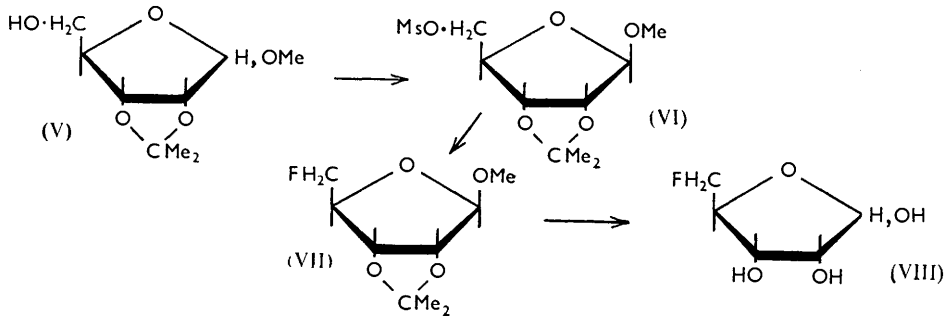
When the methanesulphonyl derivative (I) was heated with hydrated potassium fluoride in methanol at 150° for 17 hr. exchange occurred, the yield of potassium methanesulphonate being practically quantitative. A fluorine-containing product was obtained as a liquid [5] ($[\alpha]_D^{20}$ −64·5° in $CHCl_3$) which contained *O*-methyl groups (OMe, 7·3%). Acid hydrolysis of this product gave a crystalline reducing sugar containing one methoxyl

[1] Helferich and Gnüchtel, *Ber.*, 1941, **74**, 1035.
[2] Brauns, *J. Amer. Chem. Soc.*, 1923, **45**, 833, 2381; 1924, **46**, 1484; 1926, **48**, 2776; 1929, **51**, 1820.
[3] Taylor and Kent, *J.*, 1956, 2150.
[4] Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366; Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542.
[5] Taylor and Kent, *Research*, 1956, **9**, 528.

group (OMe, 15·1%). On the basis of its mutarotation, $[\alpha]_D^{20}$ +129° ⟶ +53·5° (in H_2O), the free sugar was judged to be in the cyclic α-form. The nature of these compounds will be considered in a later paper.

In experiments to avoid this methylation we investigated the suitability of other solvents for potassium fluoride. Glycerol and ethanediol proved excellent solvents for both anhydrous and hydrated potassium fluoride. Exchange readily occurs when the ester (I) is refluxed for 75 min. with anhydrous potassium fluoride in ethanediol, giving 6-deoxy-6-fluoro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose (II). Acid hydrolysis of this gave the crystalline free sugar (III) as the α-isomer, which contained no *O*-methyl group and gave a crystalline 2 : 5-dichlorophenylhydrazone. Methanolic hydrogen chloride converted either product (II) or (III) into the crystalline 6-deoxy-6-fluoro-α-D-galactopyranoside (IV). The glycoside readily consumed 2 mols. of sodium metaperiodate, and afforded the crystalline tri-*O*-methanesulphonate.

Analogous reactions were carried out with D-ribose. Methyl 2 : 3-*O*-*iso*propylidene-αβ-D-ribofuranoside (V) was converted into the crystalline ester (VI) which with anhydrous potassium fluoride in refluxing ethanediol gave the fluoride (VII), a mobile volatile liquid, in 60% yield in 1 hr. Acid hydrolysis gave 5-deoxy-5-fluoro-αβ-D-ribose (VIII) as a syrup which was chromatographically pure and was characterised as the crystalline 2 : 5-dichlorophenylhydrazone. As in the case of D-galactose, the exchange reaction in methanol gave a fluorine-containing derivative having one *O*-methyl group.



The advantages of ethanediol as a solvent are demonstrated in the case of 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranose. This affords the 6-deoxy-6-fluoro-derivative (identical with that obtained under Helferich and Gnüchtel's conditions) in good yield when refluxed with anhydrous potassium fluoride in ethanediol for 2·5 min. When heated with 1% methanolic hydrogen chloride, 6-deoxy-6-fluoro-D-glucose [1] is converted into the corresponding methyl α-pyranoside which consumed 1·85 mols. of sodium metaperiodate.

It is notable that Helferich and Gnüchtel [1] did not observe anomalous methylation in their exchange reactions in methanol. Their reaction, however, was performed at a lower temperature than ours. Treatment of the fluorodi*iso*propylidenegalactose (II) with hydrated potassium fluoride in methanol at 150° for 17 hr. afforded only unchanged starting material. No evidence of methylation was found. It is suggested that at least two reactions are involved in the exchange reactions of primary sulphonic esters with potassium fluoride in methanol.

Experimental

Paper Chromatography.—This was by downward elution on Whatman No. 1 paper with the water-poor phase of butan-1-ol–ethanol–water (4 : 1 : 5 v/v). Aldoses were detected by spraying the chromatogram with aniline hydrogen phthalate and heating it for 5—10 min. at 100°.[6]

Detection of Fluorine.—The substance (3—5 mg.) was fused with potassium, and the product

plunged into cold water (2 c.c.). After boiling with animal charcoal, the solution was filtered into a zirconium–alizarin solution [7] (0·1 c.c.). If fluorine was present the reddish-violet colour of the solution immediately changed to yellow.

The presence and analysis of fluorine in all fluoro-sugars and derivatives was confirmed by emission spectra.[8]

6-*Deoxy*-6-*fluoro*-1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*galactopyranose* (II).—6-*O*-Methanesulphonyl-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose [9] (I), m. p. 120° (15 g.), anhydrous potassium fluoride (15 g.), and ethanediol (150 c.c.) were gently refluxed for 75 min. The solution was cooled, poured into water (750 c.c.), filtered, and extracted with ether (3 × 200 c.c.). The dried extract (Na_2SO_4) when evaporated gave a syrup (9 g.) which on distillation furnished 6-*deoxy*-6-*fluoro*-1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*galactose* (5·6 g.), b. p. 70—72°/0·015 mm., n_D^{20} 1·4475, $[\alpha]_D^{20}$ −51·4° (*c* 1·284 in $CHCl_3$) (cf. 1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose, n_D^{20} 1·4680, $[\alpha]_D^{20}$ −54·7° in $CHCl_3$ [10]) (Found: C, 55·1; H, 7·0; F, 7·0. $C_{12}H_{19}O_5F$ requires C, 55·0; H, 7·2; F, 7·2%).

Methyl 6-*Deoxy*-6-*fluoro*-α-D-*galactopyranoside* (IV).—6-Deoxy-6-fluoro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose (2 g.) was refluxed in 1% methanolic hydrogen chloride (100 c.c.) for 5 hr. The solution was neutralised with lead carbonate, filtered, and evaporated to a non-reducing syrup. This was dissolved in a little acetone, the whole was filtered and ether was added. Gradually, at room temperature, crystals separated (0·35 g.). Methyl 6-deoxy-6-fluoro-α-D-galactopyranoside recrystallised from acetone–ether as needles, m. p. 139°, $[\alpha]_D^{20}$ +194° (*c* 0·103 in H_2O) (cf. methyl α-D-galactopyranoside,[11] $[\alpha]_D^{20}$ +196° in H_2O) (Found: C, 43·0; H, 6·7; OMe, 15·7; F, 9·5. $C_7H_{13}O_5F$ requires C, 42·8; H, 6·6; OMe, 15·8; F, 9·7%). Treatment of the *fluorogalactoside* with methanesulphonyl chloride in dry pyridine gave a crystalline *tri*-O-*methanesulphonate* which recrystallised from ethanol as needles, m. p. 185° (Found: C, 28·2; H, 4·4; F, positive. $C_{10}H_{19}O_{11}S_3F$ requires C, 28·0; H, 4·4%).

6-*Deoxy*-6-*fluoro*-α-D-*galactopyranose* (III).—6-Deoxy-6-fluoro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-galactopyranose (2 g.) was heated in methanol (30 c.c.) and 0·02N-sulphuric acid (50 c.c.) at 100° for 4 hr. After neutralisation with 0·1N-barium hydroxide and filtration the solution was extracted with ether (2 × 100 c.c.). The aqueous layer was evaporated under reduced pressure to a syrup (0·75 g.) which was dissolved in absolute methanol–ether. 6-*Deoxy*-6-*fluoro*-α-D-*galactopyranose* gradually separated and recrystallised from ethanol–ether as needles, m. p. 160°, $[\alpha]_D^{20}$ +135° ⟶ +76·5° (*c* 0·967 in H_2O), R_F 0·25 (cf. α-D-galactopyranose,[12] $[\alpha]_D^{20}$ +140° ⟶ +81·7°, R_F 0·1) (Found: C, 39·12; H, 5·9; F, 10·0. $C_6H_{11}O_5F$ requires C, 39·5; H, 6·04; F, 10·4%).

The 2 : 5-*dichlorophenylhydrazone* was prepared by dissolving the free sugar (50 mg.) in absolute methanol (15 c.c.), adding 2 : 5-dichlorophenylhydrazine (50 mg.), and evaporating the solution to dryness on the boiling-water bath. Ether was added to the residue and the solid hydrazone crystallised from aqueous methanol as needles, m. p. 182° (Found: C, 42·3; H, 4·35; N, 8·1; F, positive. $C_{12}H_{15}O_4N_2Cl_2F$ requires C, 42·2; H, 4·4; N, 8·2; F, 5·6%).

Methyl 5-O-*Methanesulphonyl*-2 : 3-O-iso*propylidene*-β-D-*ribofuranoside* (VI).— Methyl 2 : 3-*O*-*iso*propylidene-αβ-D-ribofuranoside,[13] b. p. 83—85°/0·05 mm. (5·5 g.), was dissolved in dry pyridine (25 c.c.) containing methanesulphonyl chloride (5 c.c.) at −18°. The solution was set aside for 24 hr. at 2°, then poured into water (300 c.c.) and extracted with chloroform (3 × 150 c.c.). The extract was washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. After drying (Na_2SO_4), the solvent was removed *in vacuo* to leave a thick yellow syrup (8·6 g.) which crystallised spontaneously. The *product* recrystallised from methanol as needles (5 g.), m. p. 82°, $[\alpha]_D^{20}$ −56·7° (*c* 1·2 in MeOH) (Found: C, 42·5; H, 6·4; S, 11·1. $C_{10}H_{18}O_7S$ requires C, 42·1; H, 6·4; S, 11·4%). The ribofuranoside was assigned the β-configuration on the basis of its negative rotation.

Methyl 5-*Deoxy*-5-*fluoro*-2 : 3-O-iso*propylidene*-β-D-*ribofuranoside* (VII).—Methyl 5-*O*-methanesulphonyl-2 : 3-*O*-*iso*propylidene-β-D-ribofuranoside (4·5 g.) in ethanediol (45 c.c.) and

[6] Partridge, *Biochem. J.*, 1948, **42**, 238.
[7] Vogel, " Qualitative Inorganic Analysis," Longmans Green and Co., London, 1947, p. 272.
[8] Birks, *Spectrochim. Acta*, 1954, **6**, 169.
[9] Helferich, Dressler, and Griebel, *J. prakt. Chem.*, 1939, **153**, 285.
[10] Ohle and Berend, *Ber.*, 1925, **58**, 2585.
[11] Riiber, Minsaas, and Lyche, *J.*, 1929, 2173.
[12] Tanret, *Bull. Soc. chim. France*, 1896, **15**, 195.
[13] Levene and Stiller, *J. Biol. Chem.*, 1934, **104**, 299.

anhydrous potassium fluoride (4·5 g.) was refluxed gently ($CaCl_2$ tube) for 1 hr. The solution was cooled and poured into water (200 c.c.) and extracted with ether (2 × 200 c.c.). The extract was dried (Na_2SO_4) and evaporated (bath-temperature, 40°) to a mobile liquid, which on distillation gave the *fluororiboside* (VIII) (1·5 g.), b. p. 32°/0·025 mm., n_D^{20} 1·4270, $[\alpha]_D^{20}$ −91·9° (*c* 1·097 in $CHCl_3$) (Found: C, 52·8; H, 7·4; OMe, 14·4; F, 9·0. $C_9H_{15}O_4F$ requires C, 52·5; H, 7·3; OMe, 15·05; F, 9·2%).

5-*Deoxy*-5-*fluoro*-αβ-D-*ribose* (VIII).—Methyl 5-deoxy-5-fluoro-2 : 3-*O*-*iso*propylidene-β-D-ribofuranoside (0·5 g.) was heated on a boiling-water bath with 0·02N-sulphuric acid (15 c.c.) for 3 hr. The solution was neutralised with 0·1N-barium hydroxide, and the filtrate extracted with ether (2 × 50 c.c.). The aqueous layer was evaporated to dryness *in vacuo*, giving 5-deoxy-5-fluoro-αβ-D-ribose as a colourless reducing syrup (0·3 g.), R_F 0·4 (cf. D-ribose, 0·22). The 2 : 5-*dichlorophenylhydrazone*, made as above, crystallised on addition of light petroleum (b. p. 40—60°) to the ether solution as needles, m. p. 130° (Found: C, 42·5; H, 4·2; N, 8·8; F, 6·0. $C_{11}H_{13}O_3N_2Cl_2F$ requires C, 42·4; H, 4·2; N, 9·0; F, 6·1%).

3 : 5-O-*Benzylidene*-6-*deoxy*-6-*fluoro*-1 : 2-O-iso*propylidene*-D-*glucofuranose*.—3 : 5-*O*-Benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranose [1] (0·5 g.) was heated in ethanediol (5 c.c.) containing anhydrous potassium fluoride (0·5 g.) at the b. p. for 2·5 min. The dark solution was poured into water (75 c.c.) and extracted with ether (2 × 50 c.c.). Evaporation of the extract gave a syrup which, crystallised from methanol (yield 0·3 g.), had $[\alpha]_D^{20}$ +32·4° (c 1·9 in MeOH), m. p. 104—105° alone or in admixture with compound formed by methanolic exchange [1] (Found: C, 61·7; H, 5·6; F, positive. Calc. for $C_{16}H_{19}O_5F$: C, 61·9; H, 6·1%).

Methyl 6-*Deoxy*-6-*fluoro*-α-D-*glucopyranoside*.—6-Deoxy-6-fluoro-D-glucose [1] (0·5 g.) was heated with 1% (w/v) methanolic hydrogen chloride (40 c.c.) for 5 hr. Neutralisation with silver carbonate, filtration, and evaporation gave a syrup from which the *product* crystallised on addition of dry chloroform–light petroleum. It had m. p. 109—110°, $[\alpha]_D^{21}$ +43° (*c* 1·76 in H_2O) (Found: C, 42·7; H, 6·5; F, 10·0. $C_7H_{13}O_5F$ requires C, 42·8; H 6·7; F, 9·7%).

Periodate Oxidations.—0·1M-Sodium metaperiodate (10 c.c.) was added to solutions of methyl α-D-galactopyranoside (24·6 mg. in 10 c.c. of water), methyl 6-deoxy-6-fluoro-α-D-galactopyranoside (7·7 mg. in 10 c.c.), and methyl 6-deoxy-6-fluoro-α-D-glucopyranoside (25 mg. in 10 c.c.) all in glass-stoppered brown bottles. After intervals 2 c.c. portions were removed and immediately transferred into 3 c.c. of M-sodium hydrogen carbonate solution and 2 c.c. of 0·5M-potassium iodide. The iodine liberated was titrated with 0·05M-sodium thiosulphate. Results were as tabulated.

Methyl α-D-*galactopyranoside*.

Time (min.)	5	10	20	30	(24 hr.)
$NaIO_4$ consumed (mols.)	0·05	0·25	0·75	1·32	2·08

Methyl 6-*deoxy*-6-*fluoro*-α-D-*galactopyranoside*.

Time (min.)	5	10	20	30	(24 hr.)
$NaIO_4$ consumed (mols.)	1·6	1·8	1·9	1·99	1·99

Methyl 6-*deoxy*-6-*fluoro*-α-D-*glucopyranoside*.

Time (min.)	5	10	20	30	(24 hr.)
$NaIO_4$ consumed (mols.)	1·3	1·4	1·7	1·8	1·85

The authors thank Sir Rudolph Peters and Mr. D. R. Davies for their help and encouragement, Mr. F. T. Birks for performing spectrometric determinations of fluorine, and Mr. E. A. Vincent for technical collaboration.

DEPARTMENT OF BIOCHEMISTRY UNIVERSITY OF OXFORD. [*Received, May 13th,* 1957.]