479. *Fluorocarbohydrates. Part IX.* Synthesis of (±)-2-Deoxy-2-fluoropentitols and Related Compounds.*

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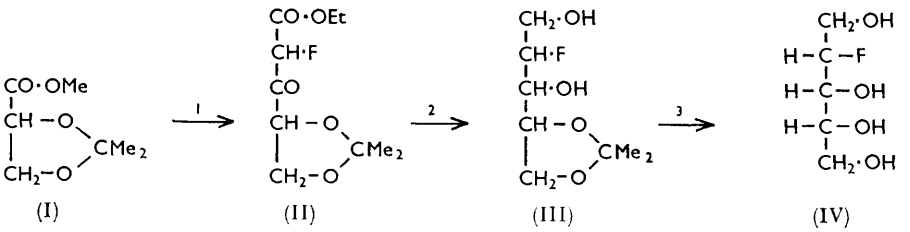
Methyl isopropylidene-DL-glycerate undergoes a Claisen-type condensation with ethyl fluoroacetate to give a mixture of isomeric ethyl 2-deoxy-2-fluoro-4,5-*O*-isopropylidene-3-oxo-(±)-pentonates which, with potassium borohydride in ethanol, gives the corresponding fluoropentitols. Hydrolysis and chromatographic separation led to 2-deoxy-2-fluoro-(±)-ribitol as a crystalline derivative, structurally related to ribitol. Reduction of 5-deoxy-5-fluoro-D-ribose gives 1-deoxy-1-fluoro-L-ribitol.

Previous investigations [1-5] support the view that stable carbohydrate analogues can exist in which one or more hydroxyl groups have been replaced by fluorine. It has been possible to synthesise fluorinated analogues of glycerol [2,6] and erythritol [2] as stable compounds giving rise to well-defined derivatives. The present work is concerned with higher homologues and in particular with the introduction of fluorine into non-terminal positions of pentose-like molecules. Fluorine has been successful introduced at C-2 of the pre-existing pentose skeleton of some nucleosides.[7] The free fluoro-sugars, however, are as yet not known. It has now been found, however, that a route to total synthesis of related pentitols exists *via* Claisen condensations with esters of glyceric acid.

* Part VIII, previous Paper.

[1] Helfrich and Gnütchtel, *Ber.*, 1941, **74**, 1035.
[2] Kent and Taylor, *J.*, 1956, 2150.
[3] Taylor and Kent, *J.*, 1958, 872.
[4] Kent, Hebblethwaite, and Taylor, *J.*, 1960, 106.
[5] Cherry and Kent, *J.*, 1962, 2507.
[6] Gryskiewicz-Trochimowski, *Rec. Trav. chim.*, 1947, **66**, 427.
[7] Codington, Doerr, Praag, Bendich, and Fox, *J. Amer. Chem. Soc.*, 1961, **83**, 5030.

Methyl isopropylidene-DL-glycerate [8] (I), obtained as a stable volatile liquid in high purity, readily condensed with ethyl fluoroacetate in the presence of sodium. Under controlled conditions, satisfactory yields of ethyl 2-deoxy-2-fluoro-4,5-*O*-isopropylidene-3-oxo-(±)-pentonates (II) were obtained.



1. $CH_2F·CO·OEt$; Na. 2. KBH_4. 3. H_2SO_4.

The fluoro-ester (II), having two asymmetric centres at C-2 and C-4 was considered to be a mixture of two racemic substances which were not separated. Reduction of the fluoro-ester with potassium borohydride (2 moles) in hot ethanol [9] gave a mixture of 2-deoxy-2-fluoro-4,5-*O*-isopropylidene-(±)-pentitols (III) of which four racemic pairs must be considered to exist, none of which could be separated at this stage. Chromatographic analysis on cellulose acetate strips [10] indicated that the substances moved as a single band. Infrared (i.r.) spectral analysis of the 2-deoxy-2-fluoro-4,5-*O*-isopropylidene-pentitols showed absence of carbonyl peak at 5·7 μ and the appearance of new peaks at 2·8 (OH) and 8—9 μ (OH).

Cleavage of the isopropylidene residue with hot dilute sulphuric acid led to the mixed (±)-2-deoxy-2-fluoropentitols. Paper chromatographic analysis indicated the presence of two major constituents having $R_{glucose}$ 2·47 and 2·82 in butan-1-ol–ethanol–water. The mixture of 2-deoxy-2-fluoropentitols had an i.r. spectrum, similar to that of ribitol but exhibiting a modified absorption in the region 8·5—10 μ.

The mixed fluoropentitols were fractionated on a cellulose-powder column [11] by elution with butanol–ethanol–water–ammonia. Two fractions were obtained, the first of which was induced to crystallise by isomorphic nucleation with ribitol. (±)-2-Deoxy-2-fluoro-ribitol (IV) was thus obtained as a pure compound containing 12% of fluorine (calculated, 12·3%), moving as a single spot in several chromatographic solvents, which on oxidation with sodium metaperiodate consumed two moles of the oxidant and gave an aldehydic product chromatographically identical with 2-deoxy-2-fluoro-(±)-glyceraldehyde. The crystalline fluoropentitol (IV) was shown by *X*-ray analysis to be very similar to ribitol and markedly different from xylitol and DL-arabitol. On the basis of these results and the isomorphorous behaviour with ribitol, the fluoropentitol (IV) is provisionally assigned a *ribo*-configuration. The similarity in the crystalline structures of ribitol and its 2-fluoro-analogue is in keeping with earlier observations [2,5] on erythritol and 2-deoxy-2-fluoroerythritol.

Reduction of 5-deoxy-5-fluoro-D-ribose [3] with potassium borohydride in the cold or with Raney nickel in ethanol [12] led to crystalline 1-deoxy-1-fluoro-L-ribitol, which on oxidation consumed 2·9 mol. of periodate.

Experimental

Paper Partition Chromatography.—This was carried out by downward elution on Whatman No. 1 paper, the water-poor phase of butan-1-ol–ethanol–water (4 : 1 : 5 v/v) being used except

[8] Ott and Kramer, *J. prakt. Chem.*, 1933, **137**, 255.
[9] Barnett and Kent, *J.*, 1963, 2743.
[10] Barnett and Kent, *Nature*, 1961, **192**, 556.
[11] Hough, Jones, and Wadman, *J.*, 1949, 2511.
[12] Karabinos and Ballou, *J. Amer. Chem. Soc.*, 1953, **75**, 4501.

where otherwise stated. *O*-Isopropylidene derivatives were examined chromatographically on cellulose acetate strips.[10] Oxidisable substances were detected on chromatograms by using sodium metaperiodate–benzidine,[13] and reducing sugars by means of silver nitrate in acetone followed by methanolic potassium hydroxide.[14]

Ethyl 2-Deoxy-2-fluoro-4,5-O-isopropylidene-3-oxo-(±)-pentonates (II).—Freshly distilled methyl *O*-isopropylidene-(±)-glycerate [8] (1·30 g., 0·19 mol.; b. p. 36—38°/0·05 mm., n_D^{19} 1·4250, cellulose acetate R_F 0·05) was added dropwise to a stirred suspension of sodium powder in ether (20 ml.). The ether was removed under reduced pressure at 0°, and redistilled ethyl fluoroacetate [15] (20 g., 0·19 mol.; b. p. 117—119°, n_D^{18} 1·3780) was added dropwise. Dry ethanol (0·5—1 ml.) was added to initiate the reaction which soon became very vigorous. The temperature was strictly maintained near 0° throughout. After the evolution of hydrogen had ceased (about 4 hr.) the mixture was left for 20 hr. at room temperature. Ether (150 ml.) was added and the reaction mixture neutralised (5N-sulphuric acid, 25 ml.) at −18°. Saturated sodium hydrogen carbonate was then added and the ethereal layer was removed. The aqueous solution was re-extracted with ether (2 × 50 ml.), and the total combined ethereal extracts were washed with sodium hydrogen carbonate and then water, and finally dried ($MgSO_4$). After removal of solvent the residual oil was fractionally distilled giving unchanged methyl *O*-isopropylidene-DL-glycerate (20 g.; b. p. 51—56°/0·08 mm.), ethyl (±)-2,4-difluoro-3-oxobutanoate [9] (5 g.; b. p. 67—80°, 0·11 mm.), and *ethyl 2-deoxy-2-fluoro-4,5-O-isopropylidene-3-oxo-(±)-pentonates* (II) (8·1 g.; b. p. 78—82/0·25 mm., n_D^{22} 1·4380, R_F 0·84. On cellulose acetate, R_F 0·15) (Found: C, 51·3; H, 6·4; F, 7·8. $C_{10}H_{15}FO_5$ requires C, 51·3; H, 6·4; F, 8·1%).

2-Deoxy-2-fluoro-4,5-O-isopropylidene-(±)-pentitols (III).—The fluoro-ester (II) (5 g., 0·21 mol.), dissolved in dry ethanol (10 ml.), was added slowly during 30 min. to potassium borohydride (3 g., 0·55 mol.) in dry ethanol at 0°. After 30 min., the temperature was raised to 70° for 5 hr. The ethanol was removed (15°/0·01 mm.), and ether (80 ml.) and water (10 ml.) were added. The separated ether layer was washed with sodium hydrogen carbonate (10 ml.), and the combined aqueous layer re-extracted with ether (3 × 100 ml.) and finally with ether in a continuous extractor for 18 hr. The total combined ethereal extracts were dried ($MgSO_4$). Removal of the solvent gave the mixed isomer of *2-deoxy-2-fluoro-4,5-O-isopropylidene-(±)-pentitols* (III) (2·1 g., 50% yield; b. p. 80—82/0·006 mm., n_D^{16} 1·5440, R_F 0·79. On cellulose acetate, R_F 0·60) (Found: C, 49·8; H, 7·95; F, 10·2. $C_8H_{15}FO_4$ requires C, 49·5; H, 7·6; F, 9·9%).

2-Deoxy-2-fluoro-(±)-pentitols.—The above fluoro-derivative (III) (1·4 g., 0·007 mol.) was dissolved in 0·2N-sulphuric acid (25 ml.), and the solution kept at 95° for 1 hr. After neutralisation ($BaCO_3$), filtration, evaporation to small volume, and refiltration the remaining water was removed by repeated addition and evaporation of dry ethanol. The resulting *2-deoxy-2-fluoro-(±)-pentitols* (1·1 g.) on paper chromatography showed $R_{glucose}$ 2·47 and 2·82 (cf. ribitol $R_{glucose}$ 1·63).

(±)-*2-Deoxy-2-fluororibitol* (IV).—The mixed isomers of 2-deoxy-2-fluoro-(±)-pentitols (60 mg.) was applied in 1 ml. of butan-1-ol–ethanol–water–0·88 ammonia (40/10/49/1 v/v) to a cellulose column (2·1 × 42 cm.) and eluted fractionally with this solvent at a rate of 6 ml./hr. Components were detected by paper-chromatographic examination of 0·1 ml. of each of the separated fractions (5 ml.). The first component was found in fractions 43—46, fractions 47—50 giving mixed components, and fractions 51—55 gave component 2. The faster-moving component was isolated after removal of the chromatographic solvent as a syrup which was twice crystallised from ethanol–ethyl acetate giving (±)-*2-deoxy-2-fluororibitol* (IV; 12 mg.), m. p. 90—91° (Found: C, 39·5; H, 7·2; F, 12·0. $C_5H_{11}FO_4$ requires C, 39·0; H, 7·15; F, 12·3%).

1-Deoxy-1-fluoro-L-ribitol.—5-Deoxy-5-fluoro-D-ribose [3] (0·5 g.) was reduced by potassium borohydride (0·16 g.) in ethanol (5 ml.) at 0° in 2·5 hr. After esterification and removal of methyl borate by distillation [9] the product was eluted from a cellulose column (2·1 × 42 cm.) with butan-1-ol–ethanol–water–ammonia (40 : 10 : 49 : 1). *1-Deoxy-1-fluoro-L-ribitol* (0·35 g.), obtained between 120 and 180 ml. of effluent, crystallised from ethanol and had R_F 0·38 [cf. (±)-2-deoxy-2-fluororibitol, R_F 0·35], m. p. 89—90° (Found: F, 12·1. $C_5H_{11}FO_4$ requires F, 12·3%).

[13] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[14] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[15] Bergmann and Blank, *J.*, 1953, 3786.

The same product (0·3 g.) resulted when the fluoro-ribose (0·4 g.) was heated for 1 hr. with Raney nickel (3 g.) in ethanol (25 ml.).[12]

Periodate Oxidation of Deoxyfluoropentitols.—The fluoropentitol (IV) (0·490 mg., 3·2 μmole) was dissolved in water (30 ml.). 3×10^{-3}M-potassium metaperiodate (5 ml.; 15 μmole) was added with shaking, the time noted, and the solution made up to 50 ml. to give a final concentration of 3×10^{-4}M-potassium metaperiodate solution.

The extinction was measured at 2475 Å on a Unicam S.P. 500 spectrophotometer at intervals.[16] The concentration of potassium metaperiodate and potassium iodate in the mixture at each time was calculated from a standard curve constructed from 3×10^{-4}M-potassium metaperiodate and 3×10^{-4}M-potassium iodate solutions. The following results were obtained:

	Periodate consumed (mol.)				Periodate consumed (mol.)		
Time (min.)	Ribitol	(±)-2-Deoxy-2-fluororibitol	1-Deoxy-1-fluoro-L-ribitol	Time (min.)	Ribitol	(±)-2-Deoxy-2-fluororibitol	1-Deoxy-1-fluoro-L-ribitol
2	1·23	0·54	1·06	15	2·80	2·00	2·44
5	1·71	0·97	—	60	3·58	—	2·83
7	2·17	1·19	2·00	120	3·82	2·03	—
10	2·52	1·59	2·18	24 hr.	4·16	2·14	2·90

10 ml. of the oxidised (±)-2-deoxy-2-fluororibitol were concentrated and examined paper chromatographically. The resulting 2-deoxy-2-fluoro-(±)-glyceraldehyde had R_F 0·79 [cf. (±)-glyceraldehyde 0·45], in butan-1-ol–pyridine–water (4 : 1 : 2 v/v), and moved identically with an authentic sample.

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[16] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.