421. *The Synthesis of 2-Deoxy-2-fluorotetritols and 2-Deoxy-2-fluoro-(±)-glyceraldehyde.*

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Ethyl ethoxalylfluoroacetate with potassium borohydride gives dimethyl (±)-2-fluoro-3-hydroxysuccinate; more vigorous reduction with lithium aluminium hydride results in a mixture of 2-deoxy-2-fluoro-(±)-tetritols. The isomers have been separated and the configuration of the crystalline 2-deoxy-2-fluoro-(±)-erythritol established. Both isomers yield crystalline 1 : 3 : 4-tri-*O*-toluene-*p*-sulphonates. Periodate oxidation of 2-deoxy-2-fluoro-(±)-erythritol gives 2-deoxy-2-fluoro-(±)-glyceraldehyde, possessing a labile fluorine atom.

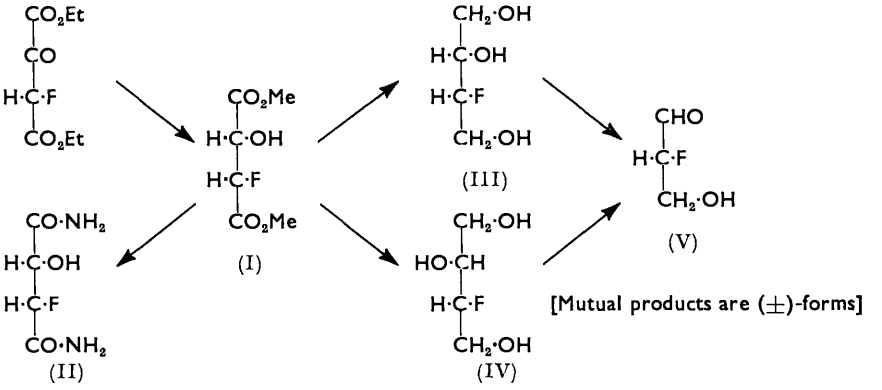
The first fluoro-carbohydrates to be reported were the 1-fluoro-compounds made by the action of anhydrous hydrogen fluoride on acetylated hexoses.[1] In these compounds the fluorine atom was sufficiently stable to permit their deacylation with sodium methoxide

[1] Brauns, *J. Amer. Chem. Soc.*, 1923, **45**, 833, 2381; 1924, **46**, 2776; 1927, **49**, 3170; 1929, **51**, 1820.

to hexosyl fluorides.[2] Later 6-deoxy-6-fluoro-D-glucose was synthesised by an exchange reaction between 3 : 5-*O*-benzylidene-6-*O*-methanesulphonyl-1 : 2-*O*-*iso*propylidene-D-glucofuranoside and hydrated potassium fluoride.[3] Both methods are limited to the introduction of the halogen into positions 1 and 6, and fluorine has not yet been introduced at other positions of the carbohydrate molecule.

We now report the total synthesis of 2-deoxy-2-fluoro-(±)-erythritol and 2-deoxy-2-fluoro-(±)-threitol and their oxidation product, 2-deoxy-2-fluoro-(±)-glyceraldehyde.[4]

Ethyl ethoxalylfluoroacetate [5] was reduced to dimethyl (±)-2-fluoro-3-hydroxysuccinate [6] with potassium borohydride. The reaction which was carried out in methanol was accompanied by trans-esterification. The fluoro-ester (I) formed a crystalline diamide



(II) and a hygroscopic disodium salt. Comparison of the infrared spectra of malamide [7] and the amide (II) indicated the presence of the C–F bond in the latter. Further reduction of the ester (I) with lithium aluminium hydride gave a syrup which was chiefly a mixture of 2-deoxy-2-fluorotetritols (III) and (IV). The same tetritols were also obtained in high yield when ethyl ethoxalylfluoroacetate itself was reduced with a large excess of lithium aluminium hydride. From the mixed tetritols at room temperature (4 days) 2-deoxy-2-fluoro-(±)-erythritol (III) crystallised spontaneously and 2-deoxy-2-fluoro-(±)-threitol (IV) was separated chromatographically from the mother-liquors. This method of separating the isomers was subsequently replaced by fractional distillation in a high vacuum. Paper-partition chromatography of the isomers (III) and (IV) gave the same R_F value (0·6).

The configuration of 2-deoxy-2-fluoro-(±)-erythritol (III) was established by an *X*-ray crystallographic comparison with erythritol. The second racemate 2-deoxy-2-fluoro-(±)-threitol (IV), isolated as a syrup, yielded a 1 : 3 : 4-tri-*O*-toluene-*p*-sulphonate (m. p. 115°) which was different from the 1 : 3 : 4-tri-*O*-toluene-*p*-sulphonate (m. p. 85°) of 2-deoxy-2-fluoro-(±)-erythritol.

Both isomers (III) and (IV) consumed 1 mol. of sodium metaperiodate (formation of formaldehyde was shown) and the highly reducing product, 2-deoxy-2-fluoro-(±)-glyceraldehyde (V), was isolated as a colourless syrup. The following evidence for its structure was obtained. (1) It reacted immediately with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, giving a high yield of a yellow amorphous hydrazone from which however fluorine had been eliminated (confirmed by emission spectrographic analysis); (2) reduction with lithium aluminium hydride gave 2-fluoropropane-1 : 3-diol (2-deoxy-2-fluoroglycerol), isolated as its crystalline 1 : 3 di-*O*-toluene-*p*-sulphonate; (3) synthesis of 3-fluoro-(±)-propane-1 : 2-diol [(±)-1-deoxy-1-fluoroglycerol] has been reported,[8]

[2] Helferich, Bauerlein, and Weigand, *Annalen*, 1926, **447**, 30; Helferich and Gootz, *Ber.*, 1929, **62**, 2505.
[3] Helferich and Gnüchtel, *Ber.*, 1941, **74**, 1035.
[4] Kent and Taylor, *Research*, 1955, **8**, s66.
[5] Rivett, *J.*, 1953, 3710.
[6] Taylor and Kent, *Nature*, 1954, **174**, 401.
[7] Freudenberg and Brauns, *Ber.*, 1922, **55**, 1352.
[8] Gryskiewicz-Trochimowski, *Rec. Trav. chim.*, 1947, **66**, 427.

though no evidence for the structure was presented; this compound was, therefore, prepared and it was found, in contrast to the above 2-deoxy-2-fluoroglycerol, to consume 0·8 mol. of sodium metaperiodate.

Although the fluorine atom in (±)-2-deoxy-2-fluoroglyceraldehyde is labile in the presence of 2 : 4-dinitrophenylhydrazine in hydrochloric acid and two mols. of 2 : 4-dinitrophenylhydrazine are consumed, no structure is yet advanced for the product, which may exist in polymorphic forms (cf. acetaldehyde [9] and fluoroacetaldehyde [10]).

Note on the X-Ray Crystallographic Analysis of 2-Deoxy-2-fluoro-(±)-erythritol (by Mr. H. M. Powell).—Examination of erythritol and 2-deoxy-2-fluoro-(±)-erythritol by single-crystal *X*-ray diffraction methods shows that they are structurally very closely related. Erythritol, which, according to early measurements,[11] belongs to the tetragonal bipyramidal (4/*m*) class of crystals, has $a = 12{\cdot}8$, $c = 6{\cdot}85$ Å. Absent reflections *hkl* for $h + k + l$ odd, *hk*0 for either *h* or *k* odd, and 00*l* for $l = 4n$, indicate the space group $I4_1/a$. This is consistent with the crystal symmetry and is supported by observations of a general inequality in intensity of the reflection *h*0*l* and its corresponding $\bar{h}0l$. In the unit cell there are eight molecules which must occupy special space-group positions so that each lies either on a two-fold symmetry axis or, more probably, in a symmetry centre.

The 2-deoxy-2-fluoro-(±)-erythritol was not recognisable from crystal shape as tetragonal, though it gave a uniaxial interference pattern. Under *X*-ray examination a unit cell was found with dimensions very similar to those of erythritol: $a = b = 12{\cdot}8$, $c = 6{\cdot}85$. A zero layer line Weissenberg photograph about the *c* axis shows no deviation from tetragonal symmetry. The general distribution of intensities among the reflections *hk*0 when both *h* and *k* are even strongly resembles that in erythritol, but a few weak reflections which have both *h* and *k* odd appear. This means that there is no glide plane *a* in the structure, although there is a pseudo-glide plane of this kind. The absence of the glide plane is shown by some inequalities in intensities of reflections *hkl* and the corresponding $hk\bar{l}$.

The great similarity of *X*-ray diffraction patterns for the two substances leaves no doubt that the arrangement of atoms in the two is almost the same, and the lowering of space-group symmetry on passing from erythritol to 2-deoxy-2-fluoro-(±)-erythritol is precisely what would be expected when molecules which occupy special symmetry positions in the unit cell have their own symmetry destroyed by substitution, although the general shape and size of the molecule and some at least of its possibilities for hydrogen bonding to its neighbours are left unaffected. The two molecules must therefore have similar configurations. A more detailed structural investigation is being made.

Experimental

Paper chromatography 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). Hydroxy-compounds were detected by spraying chromatograms with 1% aqueous potassium permanganate.[12]

Dimethyl (±)-2-Fluoro-3-hydroxysuccinate (*Methyl Fluoromalate*).—Ethyl ethoxalylfluoroacetate (10 g., 0·54 mol.)[5] in methanol (60 c.c.) was added dropwise to a stirred solution of potassium borohydride (6 g., 0·112 mol.) in methanol (60 c.c.). The temperature rose to 50°, and dropped to 25° when the reduction was complete. Stirring was continued for a further 30 min. To the resulting pale green solution excess of methanolic hydrogen chloride was added. Methyl borate was removed by distillation of the filtered solution with repeated addition of methanol. After neutralisation with lead carbonate, filtration, and concentration to dryness under reduced pressure, the product was extracted with ether. Removal of the solvent gave a colourless viscous liquid which on distillation yielded *dimethyl fluoromalate* (5 g.), b. p. 90°/0·5 mm. (Found: C, 40·0; H, 5·3. $C_6H_9O_5F$ requires C, 39·9; H, 5·0%). This gave a positive test for an α-hydroxy-group with ferric chloride–phenol. It gave an absorption maximum at 300 mμ and an infrared band at 1050 cm.$^{-1}$ (C–F).

(±)-2-*Fluoro*-3-*hydroxysuccinamide* (*Fluoromalamide*).—Dimethyl fluoromalate (0·5 g.) in

[9] Bryant, *J. Amer. Chem. Soc.*, 1933, **55**, 3201; Martin, Synge, and Bell, *Biochem. J.*, 1941, **35**, 294.
[10] Saunders, Stacey, and Wilding, *J.*, 1949, 774.
[11] Groth, "Chemische Crystallographie," Engelmann, Leipzig, 1910, Vol. III, p. 240.
[12] Pacsu, Mora, and Kent, *Science*, 1949, **110**, 446.

anhydrous methanol (10 c.c.) was saturated with ammonia at 0°. After 24 hr. at room temperature crystals separated. After a further 24 hr. at 0° the *diamide* was collected, washed with a little propan-2-ol, and recrystallised therefrom as needles (0·2 g.), m. p. 160° (Found : C, 32·1; H, 4·4; N, 18·8. $C_4H_7O_3N_2F$ requires C, 32·0; H, 4·6; N, 18·7%). Further diamide (0·08 g.) was obtained by concentrating the mother-liquor, redissolving the syrup in methanol, and saturating the solution with ammonia. A mixed m. p. with malamide [7] (m. p. 162°) showed a depression. Of malamide and fluoromalamide, only the latter gave an infrared band at 1050 cm.$^{-1}$ (C–F).

Disodium (±)-2-*Fluoro*-3-*hydroxysuccinate* (*Sodium Fluoromalate*).—Dimethyl fluoromalate (1 g.) was dissolved in water (3 c.c.) and 1·5N-sodium hydroxide (7 c.c.) gradually added with stirring. After 24 hr. at 0° the yellow solution was extracted with ether (2 × 25 c.c.), and the aqueous layer evaporated to dryness under reduced pressure. A yellow solid remained which was washed with dry ethanol (3 × 50 c.c.) and heated at 100°/11 mm. for 24 hr. The *disodium fluoromalate* (1 g.) was extremely hygroscopic and no attempts to recrystallise it were made (Found : C, 24·3; H, 1·4. $C_4H_3O_5Na_2F$ requires C, 24·5; H, 1·5%).

2-*Deoxy*-2-*fluoro*-(±)-*erythritol*.—*Method* I. Methyl fluoromalate (4 g.) in dry ether (100 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (3 g.) in ether (150 c.c.) at such a rate as to produce gentle refluxing. The mixture was stirred for a further 60 min. Excess of hydride was decomposed by water at 0°. Sulphuric acid (5N; 75 c.c.) was added with stirring, the aqueous layer separated and neutralised with magnesium carbonate, and the resulting solid mass extracted with boiling ethyl acetate–ethanol (3 : 1; 4 × 100 c.c.). The extract was filtered and dried ($MgSO_4$), and the solvent removed *in vacuo*, to leave a pale brown syrup (2 g.). Partition chromatography revealed three components (R_F 0·4, 0·6, 0·85) [butanol–ethanol–water (4 : 1 : 5) as solvent; potassium permanganate (1% solution) as developer]. In 4 days at room temperature the syrup yielded needles which were separated on a porous plate; the 2-*deoxy*-2-*fluoro*-(±)-*erythritol* (0·2 g.) recrystallised from ethyl acetate as needles, m. p. 70°, R_F 0·6 (Found : C, 39·2; H, 7·4. $C_4H_9O_3F$ requires C, 38·7; H, 7·3%).

Method II. Ethyl ethoxalylfluoroacetate [5] (16 g.) in dry ether (150 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (12 g.) in ether (400 c.c.) at such a rate that steady refluxing was maintained. The mixture was then kept at room temperature for 24 hr. The excess of hydride was decomposed by water at 0°; 5N-sulphuric acid (100 c.c.) was added with stirring, the aqueous layer separated and neutralised with magnesium carbonate, and the resulting solid extracted with boiling ethyl acetate–ethanol (3 : 1; 3 × 200 c.c.). The extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo*, to leave a pale brown syrup (8 g.), R_F 0·4, 0·6, 0·85. Distillation of the syrup gave a fraction boiling at 120°/1·4 × 10^{-2} mm. The product (4 g.) was a colourless syrup (R_F 0·6) which partly solidified overnight. The solid, separated on a porous plate, crystallised from ethyl acetate, giving colourless needles of 2-deoxy-2-fluoro-(±)-erythritol (3 g.), m. p. 70°, R_F 0·6 (Found : C, 39·0; H, 7·5%). Infrared spectra of this compound showed bands at 0·92 and 0·95 cm.$^{-1}$ which were attributed to the C–F and the –OH · · · F–C bond. The porous plate was extracted with boiling ethanol, and the extract evaporated to dryness *in vacuo*, to leave 2-deoxy-2-fluoro-(±)-threitol as a colourless syrup (0·89 g.), R_F 0·6.

2-*Deoxy*-2-*fluoro*-1 : 3 : 4-*tri*-O-*toluene*-p-*sulphonyl*-(±)-*erythritol*.—2-Deoxy-2-fluoro-(±)-erythritol (0·062 g.) in dry pyridine (5 c.c.) containing toluene-*p*-sulphonyl chloride (1 g.) was kept at room temperature for 24 hr., then poured into water (50 c.c.). The product, extracted with chloroform, washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4) and recovered by evaporation *in vacuo*, was a colourless syrup (0·2 g.). This was dissolved in propan-2-ol–ether; the 1 : 3 : 4-*tri*-O-*toluene*-p-*sulphonate* separated and recrystallised from propan-2-ol as rhombic crystals, m. p. 85° (Found : C, 51·2; H, 4·7; S, 15·2; F 3·0. $C_{25}H_{27}O_9S_3F$ requires C, 51·2; H, 4·6; S, 16·3; F, 3·2%).

2-*Deoxy*-2-*fluoro*-1 : 3 : 4-*tri*-O-*toluene*-p-*sulphonyl*-(±)-*threitol*.—The threitol (0·2 g.) in dry pyridine (10 c.c.) containing toluene-*p*-sulphonyl chloride (2 g.) yielded, as above, the 1 : 3 : 4-*tri*-O-*toluene*-p-*sulphonate* as needles, m. p. 115° (Found : C, 51·1; H, 4·4; S, 15·2; F, 3·0%).

Oxidation of 2-*Deoxy*-2-*fluoro*-(±)-*erythritol with Sodium Metaperiodate*.—The rate of oxidation of 2-deoxy-2-fluoro-(±)-erythritol was compared with that of erythritol under the following conditions. 0·1M-Sodium metaperiodate (10 c.c.) was added to a solution of the erythritol (0·062 g.) in water (10 c.c.) in a glass-stoppered brown bottle. After intervals, 2 c.c. portions were removed and transferred immediately into 3 c.c. of 0·5M-sodium hydrogen carbonate solution and 2 c.c. of 0·05M-potassium iodide. The iodine liberated was titrated with 0·05M-sodium thiosulphate.

2-Deoxy-2-fluoro-(±)-erytheritol.

Time (min.)	25	50	75	(24 hr.)
$NaIO_4$ consumed (mole/mole)	0·85	0·9	0·94	1·0

Erythritol.

Time (min.)	25	50	75	(24 hr.)
$NaIO_4$ consumed (mole/mole)	1·31	1·35	1·44	1·5

2-Deoxy-2-fluoro-(±)-glyceraldehyde (*α-Fluoro-β-hydroxypropaldehyde*).—To 2-deoxy-2-fluoro-(±)-erythritol (5·12 g.) in water (20 c.c.) was added sodium metaperiodate (8·85 g.) in water (100 c.c.), and the solution kept at room temperature for 30 min. The aqueous solution was evaporated to dryness *in vacuo* at 50° to remove formaldehyde (identified as the 2 : 4-dinitrophenylhydrazone). The residue was extracted with ether (10 × 100 c.c.), the extract dried (Na_2SO_4), and the solvent removed *in vacuo*, to leave a syrup (3·29 g.) which on distillation gave 2-deoxy-2-fluoro-(±)-glyceraldehyde, b. p. 60°/0·05 mm., n_D^{20} 1·1446 (Found : C, 39·2; H, 6·3. $C_3H_5O_2F$ requires C, 39·1; H, 5·5%). This reduced Fehling's solution on warming and gave a positive test with Schiff's reagent. With 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid it gave an immediate yellow precipitate of a fluorine-free *hydrazone*, m. p. 125° (Found : C, 40·1; H, 3·3; N, 24·4. $C_{15}H_{14}O_9N_8$ requires C, 40·0; H, 3·1; N, 24·9%). The m. p. of the hydrazone varied in different preparations (120° to 125°), which suggested polymorphism.

Reduction of 2-Deoxy-2-fluoro-(±)-glyceraldehyde with Lithium Aluminium Hydride.—The aldehyde (0·5 g.) in dry ether (100 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (2 g.) in ether (150 c.c.) Excess of hydride was decomposed by water at 0° after which 5N-sulphuric acid (30 c.c.) was added. The aqueous layer was neutralised with magnesium carbonate, the resulting solid extracted with boiling ethyl acetate–ethanol (3 : 1 v/v; 2 × 100 c.c.), and the extract dried (Na_2SO_4). Evaporation *in vacuo* left *2-fluoropropane-1 : 3-diol* (*2-deoxy-2-fluoroglycerol*) as a colourless syrup (0·3 g.). This was dissolved in dry pyridine (10 c.c.) containing toluene-*p*-sulphonyl chloride (2 g.) and kept at room temperature for 24 hr. after which it was poured into water (100 c.c.) and the syrup which separated was extracted with chloroform and isolated by the usual procedure, to give *2-fluoro-1 : 3-ditoluene-p-sulphonyloxypropane* as a brown syrup. This separated from propan-2-ol–ether as a light brown solid which crystallised (charcoal) from ethanol as needles, m. p. 109° (Found : C, 50·6; H, 4·5; S, 14·6; F, 4·5. $C_{17}H_{19}O_6S_2F$ requires C, 50·7; H, 4·7; S, 15·9; F, 4·7%).

Oxidation of Isomeric Fluoroglycerols with Sodium Metaperiodate.—The rates of oxidation of glycerol, 2-deoxy-2-fluoroglycerol, and 1-deoxy-1-fluoro-(±)-glycerol[8] (b. p. 42—45°/0·05 mm., n_D^{20} 1·4198) were compared under the conditions described for 2-deoxy-2-fluoro-(±)-erythritol.

Glycerol.

Time (min.)	6	27	50	96
$NaIO_4$ consumed (mole/mole)	1·2	1·3	1·4	1·4

1-Deoxy-1-fluoro-(±)-glycerol.

Time (min.)	2	23	46	91
$NaIO_4$ consumed (mole/mole)	0·68	0·75	0·8	0·8

2-Deoxy-2-fluoroglycerol.

Time (min.)	3	29	62	120
$NaIO_4$ consumed (mole/mole)	0·16	0·17	0·17	0·17

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