477. *Fluorocarbohydrates. Part V.* Methyl (±)-2-Deoxy-2-fluoroerythronate and Related Compounds.*

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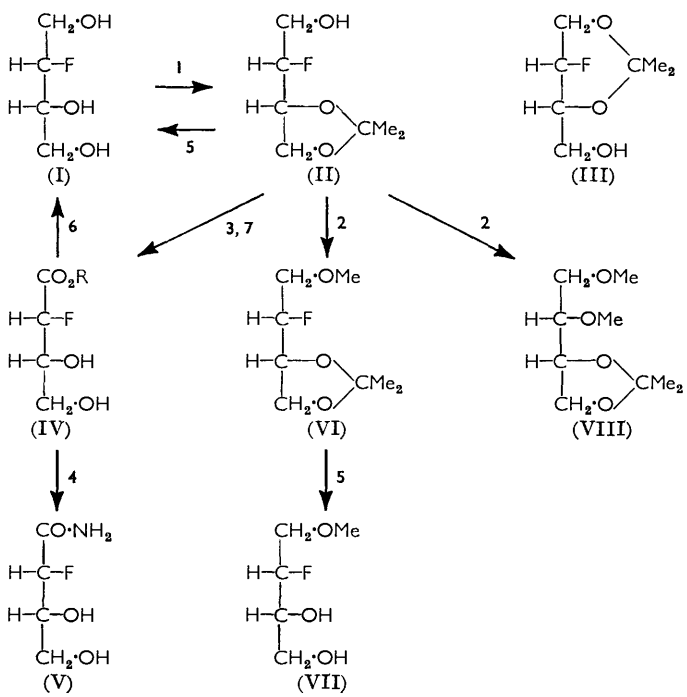
(±)-2-Deoxy-2-fluoroerythritol gives a liquid 3,4-*O*-isopropylidene derivative whose structure has been demonstrated by methylation and periodate oxidation. Vigorous methylation with silver oxide and methyl iodide is accompanied by expulsion of fluorine and the formation of a 1,2-di-*O*-methyl ether. Oxidation of the fluoroisopropylidene derivative gives the corresponding carboxylic acid from which a methyl hydroxy-ester and crystalline amide have been obtained. (±)-2-Deoxy-2-fluorothreitol forms similar isopropylidene derivatives.

(±)-2-Deoxy-2-fluoroerythritol is a highly crystalline compound, readily separable from the corresponding (±)-fluorothreitol;[1] its configuration is known from *X*-ray diffraction data.[2] It is thus a convenient starting point for synthesis of related fluorocarbohydrates of the *erythro*-series. The 2-deoxy-fluoroerythritol (I) forms an isopropylidene derivative under the usual conditions, the structure of which may involve a 3,4- (II) or a 1,3-ring (III). The following evidence conclusively establishes that the structure (II) is correct:



Reagents: 1, Me_2CO–H_2SO_4. 2, MeI–Ag_2O. 3, $Ba(MnO_4)_2$. 4, NH_3–MeOH. 5, H^+–H_2O. 6, Na–Mg. 7, H^+–MeOH. All products are (±)-forms.

(*a*) The ketal forms a toluene-*p*-sulphonate (not crystalline) which exchanges with iodide under the conditions of the Oldham and Rutherford reaction,[3] consistently with the presence of a primary alcohol group in the molecule. (*b*) Gentle methylation, with Purdie's

* Part IV, *J.*, 1962, 2266.

[1] Taylor and Kent, *J.*, 1956, 2150.
[2] Bekoe and Powell, *Proc. Roy. Soc.*, 1959, *A*, **250**, 301.
[3] Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366.

reagents, gives a monomethyl ether, which after removal of the isopropylidene group, is susceptible to oxidation with periodate, 0·8 mol. being consumed in 24 hours. (*c*) The crystalline amide of the corresponding fluoroerythronic acid fails to give a positive reaction in the Weerman test, indicating the absence of a 2-hydroxyl group.

The isopropylidene derivative appears to behave normally towards aqueous acid hydrolysis, the parent fluoroerythritol being obtained quantitatively with 0·2M-sulphuric acid at 95° in 45 min.

The course of methylation of the compound (II) with silver oxide and methyl iodide is of interest. Initially, the compound shows, *inter alia*, strong absorption bonds at 3600 (OH) and 1070 cm.$^{-1}$ (F), and repeated methylation leads to the expected progressive disappearance of the hydroxyl band. When this has been completely extinguished, the product is fluorine-free and contains two *O*-methyl groups (VIII). It is considered that, under exhaustive conditions, the secondary fluorine atom is replaced by hydroxyl which is then methylated. After three methylations, the required methyl fluoro-compound (VI) was obtained, the conditions being comparable with those employed for the etherification of methyl 6-deoxy-6-fluoro-α-D-galactoside.[4] The isopropylidene group is readily removed by hot 0·02M-sulphuric acid, giving (±)-2-deoxy-2-fluoro-1-*O*-methylerythritol as a distillable colourless liquid, which can be oxidised [5] by aqueous sodium metaperiodate at room temperature.

Reaction of 2-deoxy-2-fluoroisopropylidene-erythritol (II) with barium permanganate leads to oxidation of the primary alcoholic group at position 1 and the formation of the corresponding fluoroerythronic acid. This was converted, with hydrolysis, into the methyl ester (IV; R = Me) and thence into the crystalline amide (V). The ester (IV; R = Me) does not appear to lactonize easily when heated either at atmospheric or reduced pressures. It is reduced by sodium amalgam [6,7] in the presence of sodium hydrogen oxalate to the parent (±)-2-deoxy-2-fluoroerythritol (I).

The reaction of (±)-2-deoxy-2-fluorothreitol with acetone follows a course similar to that of the *erythro*-isomer.

Experimental

Chromatography.—This was performed by downward elution on Whatman no. 1 paper with butan-1-ol–ethanol–water (4 : 1 : 5). Hydroxylic compounds were detected by 1% potassium permanganate in 2% aqueous sodium carbonate.

Fluorine Analyses.—These were performed by the method of Belcher, Leonard, and West.[8]

Reaction of (±)-2-*Deoxy*-2-*fluoroerythritol* (I) *with Acetone.*—The fluoro-compound (3 g.) was shaken with acetone (180 ml.) containing concentrated sulphuric acid (0·5% w/v) for 18 hr. at room temperature. After neutralization with sodium carbonate, the resulting (±)-2-*deoxy*-2-*fluoro*-3,4-*isopropylidene-erythritol* (II) (3 g., 76%) was distilled; it had b. p. 44°/0·1 mm., n_D^{18} 1·4322 (Found: C, 51·1; H, 8·1; F, 10·8. $C_7H_{13}FO_3$ requires C, 51·2; H, 7·9; F, 11·6%). The same compound was obtained in 50% yield by the use of acetone and phosphorus pentoxide for 2 hr. at room temperature.

Methyl (±)-2-*Deoxy*-2-*fluoroerythronate* (IV; R = Me).—The above isopropylidene derivative (II) (1·76 g.) was added to a solution of barium permanganate (4·28 g.) and barium hydroxide (2·66 g.) in water (200 ml.). After 24 hr. at room temperature the excess of oxidant was removed from the filtered solution by addition of the minimal amount of 1% formic acid. After further filtration, the solution was evaporated to dryness at 35°, giving the barium salt (0·9 g.) of the fluoro-acid (IV; R = $Ba_{\frac{1}{2}}$). The dried salt was treated with methanolic sulphuric acid (4% w/v) and the barium sulphate was removed. More methanolic sulphuric acid (4 ml.) was added and the solution was refluxed for 18 hr. After neutralization with barium carbonate

[4] Kent, Morris, and Taylor, *J.*, 1960, 298.
[5] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[6] Isbell, Frush, and Holt, *J. Res. Nat. Bur. Standards*, 1954, **53**, 217; Schaffer and Isbell, *ibid.*, 1956, **57**, 333.
[7] Isbell, Frush, and Holt, *J. Res. Nat. Bur. Standards*, 1960, **64**, 135.
[8] Belcher, Leonard, and West, *J.*, 1959, 3577.

and filtration, the solvent was removed, giving *methyl* (±)-2-*deoxy*-2-*fluoroerythronate* (0·3 g.) n_D^{18} 1·4479 (Found: C, 39·2; H, 6·0; F, 11·8; OMe, 19·9. $C_5H_9FO_4$ requires C, 39·5; H, 5·9; F, 12·5; OMe, 20·4%).

(±)-2-*Deoxy*-2-*fluoroerythronamide* (V).—The fluoro-ester (IV; R = Me) (0·1 g.), when treated with saturated methanolic ammonia (1·5 ml.) for 24 hr. at 0°, gave the *amide* (V), m. p. 103° (from acetone) (Found: C, 35·0; H, 5·8; F, 12·9; N, 10·1. $C_4H_8FNO_3$ requires C, 35·0; H, 5·8; F, 13·9; N, 10·2%).

Reduction of Methyl (±)-2-*Deoxy*-2-*fluoroerythronate* (IV; R = Me).—The ester (0·2 g., 1 mmole), dissolved in ice–water (20 ml.), was stirred with sodium hydrogen oxalate (1·97 g.) and 5% sodium amalgam (4·49 g.). When all the amalgam had been used, the solution was adjusted to pH 8 with 0·1N-sodium hydroxide. After addition of methanol (3 vol.) the filtered solution was concentrated and passed successively down Amberlite IR-120H and Duolite A-4 ion-exchange columns.[7] The eluted solution and washings (250 ml.) were concentrated to a syrup, from which crystals of (±)-2-deoxy-2-fluoroerythritol (I), R_F 0·5, m. p. 71—72° alone or in admixture with authentic material, were obtained.

(±)-2-*Deoxy*-2-*fluoro*-3,4-O-*isopropylidene*-1-O-*methylerythritol* (VI).—(i) The isopropylidene derivative (II) (0·56 g.) was repeatedly methylated (5 times in all) for 12 hr., each time with methyl iodide (1 ml.) and silver oxide (0·3 g.). A fluorine-free product, (±)-3,4-O-*isopropylidene*-1,2-*di*-O-*methyl*-*erythritol* (VIII) (0·3 g.), b. p. 49°/25 mm., n_D^{18} 1·4128, was obtained (Found: C, 56·7; H, 9·0; OMe, 32·0. $C_9H_{18}O_4$ requires C, 56·7; H, 9·4; OMe, 32·6%).

(ii) The isopropylidene derivative (II) (0·55 g.) was methylated thrice with methyl iodide (8 ml.) and silver oxide (0·3 g.), for 8 hr. each time. The change in the absorption band at 3520 cm.$^{-1}$ (OH) was observed between each methylation. The resulting (±)-2-*deoxy*-2-*fluoro*-3,4-O-*isopropylidene*-1-O-*methylerythritol* (VI) was a colourless syrup, b. p. 49°/25 mm. (0·5 g., 83%), n_D^{18} 1·4128 (Found: C, 53·3; H, 8·3; F, 9·7; OMe, 17·3. $C_8H_{15}FO_3$ requires C, 53·8; H, 8·4; F, 10·7; OMe, 17·4%).

(±)-2-*Deoxy*-2-*fluoro*-1-O-*methylerythritol* (VII).—The methyl ether (VI) (0·1 g.) was hydrolyzed at 100° for 2 hr. with 0·02M-sulphuric acid (3 ml.). The neutralized solution (barium carbonate) was filtered and concentrated, giving (±)-2-*deoxy*-2-*fluoro*-1-O-*methyl*-*erythritol* (VII), R_F 0·7, n_D^{20} 1·4436 (Found: OMe, 21·8; F, 12·6. $C_5H_{11}FO_3$ requires OMe, 23·2; F, 13·8%).

Periodate Oxidation.—The fluoro-alcohol (4 mg.) was dissolved in 100 ml. of 3×10^{-4}M-sodium metaperiodate at 24°. The rate of oxidation was followed by the changes in optical density at 2475 Å, by using a Cary recording ultraviolet spectrophotometer. Results were as tabulated.

(±)-2-*Deoxy*-2-*fluoroerythritol.*

Time (min.)	2	4	10	25	40	55	70	85	120	(24 hr.)
$NaIO_4$ consumed (mole/mole)	0·14	0·23	0·43	0·65	0·76	0·82	0·86	0·88	0·91	1

(±)-2-*Deoxy*-2-*fluoro*-1-O-*methylerythritol.*

Time (min.)	2	4	10	25	40	55	70	85	120	(24 hr.)
$NaIO_4$ consumed (mole/mole)	0·07	0·13	0·27	0·48	0·57	0·63	0·67	0·71	0·74	0·79

(±)-2-*Deoxy*-2-*fluoro*-3,4-O-*isopropylidenethreitol.*—This was prepared from (±)-2-deoxy-2-fluorothreitol (4·8 g.; n_D^{18} 1·4620) by using acetone–sulphuric acid as described for the corresponding erythritol compound. The *product* (3·9 g., 60%) had b. p. 102°/25 mm., n_D^{18} 1·4372 (Found: C, 51·8; H, 7·8; F, 11·5. $C_7H_{13}FO_3$ requires C, 51·2; H, 7·9; F, 11·6%).

(±)-2-*Deoxy*-2-*fluoro*-1-O-*methylthreitol.*—The preceding isopropylidene derivative was methylated by the above method (ii), then hydrolysed as described for the corresponding fluoroerythritol compounds. The resulting *ether* was a colourless syrup, R_F 0·63, n_D^{18} 1·4446 (Found: C, 43·4; H, 7·6; F, 12·7; OMe, 23·9. $C_5H_{11}FO_3$ requires C, 43·5; H, 8·9; F, 13·8; OMe, 23·2%). The product was oxidisable with sodium metaperiodate.

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