

20. Fluorocarbohydrates. Part II.* Characterisation of (\pm)-2-Deoxy-2-fluoroglyceric Acid and its Quinine Salts.

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The conditions for oxidation of (\pm)-2-deoxy-2-fluoroglyceraldehyde have been studied. The aldehyde is quantitatively oxidised by hypohalites to the acid, which has been characterised as the methyl ester and crystalline amide. With quinine, a pair of salts corresponding to (+ -) and (- -) forms was obtained.

In Part I* syntheses of 6-deoxy-6-fluoro-D-galactose and 5-deoxy-5-fluoro-D-ribose were described. Extension of the synthesis of sugars containing non-terminal fluorine required the active forms of 2-deoxy-2-fluoroglyceraldehyde or of the corresponding acid.

Attempts to obtain crystalline derivatives (hydrazones or esters) of the fluoro-aldehyde having failed,¹ the oxidation to the fluoro-acid was studied. It is reported that (\pm)-glyceraldehyde is oxidised to glyceric acid by mercuric oxide² (70% yield of barium salt), aqueous bromine³ (76% yield of acid), alkaline cupric sulphate⁴ (45% yield of calcium salt), 0.1N-iodine in sodium carbonate⁵ (calculated yield 99%). With aqueous bromine, (\pm)-2-deoxy-2-fluoroglyceraldehyde is oxidised slowly (5% in 3 hr.), with some liberation of ionic fluorine. Similar expulsion of fluoride has been noted¹ when phenylhydrazines react in acidic conditions with (\pm)-2-deoxy-2-fluoroglyceraldehyde.

In aqueous solution, the fluoro-aldehyde is oxidised rapidly by sodium or barium hypiodite. In 15 min. at 20°, complete loss of reducing power is attained, with the consumption of 1.2 mols. of oxidant. In methanol, only 25—50% oxidation is observed and the yields were not enhanced by increase of temperature (30° to 40°).

For the preparation of the fluoro-acid, aqueous barium hypiodite was employed and the product was separated as the lead salt, treatment of which with methanol and sulphuric acid yielded the volatile (\pm)-methyl 2-deoxy-2-fluoroglycerate from which a crystalline amide was obtained. Free deoxyfluoroglyceric acid, obtained from the lead salt by addition of Dowex 50, formed highly hygroscopic crystals which were separated from glyceric and other acids by paper chromatography. With quinine, the fluoro-acid gave a salt (A) which after recrystallisation had $[\alpha]_D^{21} -151^\circ \pm 2^\circ$ (m. p. 196°), and from the mother-liquors a second and more soluble salt (B) was obtained having $[\alpha]_D^{20} -131^\circ \pm 2^\circ$ (m. p. 180°). It is of interest that with the quinine salts of glyceric acid⁶ the less-soluble compound (m. p. 178—180°) is the (- -) salt and the more soluble compound ($[\alpha]_D^{20} -126^\circ$, m. p. 187—188°) is evidently the (- +) salt. Addition of calcium hydroxide to (-)-quinine (+)-glycerate gives calcium (+)-glycerate, $[\alpha]_D^{20} +11.6^\circ$.

It is tentatively concluded that the salt A is the (-)-quinine (-)-2-deoxy-2-fluoroglycerate, and salt B is the (-)-quinine (+)-2-deoxy-2-fluoroglycerate. The calcium salts of the resolved acids were relatively soluble and therefore not suitable for reference purposes.

EXPERIMENTAL

Paper Chromatography.—Aldehydes and polyols were examined by downward elution in the water-poor phase of butan-1-ol-ethanol-water (4 : 1 : 5 v/v), and acids by upward elution in propan-1-ol-ammonia (*d* 0.88) (6 : 4 v/v). Aldehydes were detected by aniline hydrogen phthalate,⁷ polyols by potassium permanganate,⁸ and acids by Bromocresol Green.⁹

* Part I, *J.*, 1958, 872.

¹ Taylor and Kent, *J.*, 1956, 2150.

² Wohl and Schellenberg, *Ber.*, 1922, **55**, 1404.

³ Baer, Grosheintz, and Fischer, *J. Amer. Chem. Soc.*, 1939, **61**, 2607.

⁴ Wohl and Neuberg, *Ber.*, 1900, **33**, 3102; Nef, *Annalen*, 1904, **335**, 323.

⁵ Cajori, *J. Biol. Chem.*, 1922, **54**, 617; Spoehr and Strain, *ibid.*, 1930, **89**, 503.

⁶ Anderson, *Amer. Chem. J.*, 1909, **42**, 401.

⁷ Partridge, *Biochem. J.*, 1948, **42**, 238.

⁸ Pacsu, Mora, and Kent, *Science*, 1949, **110**, 446.

⁹ Brown and Hall, *Nature*, 1950, **166**, 66; *Biochem. J.*, 1950, **47**, 598.

Detection of Fluoride.—Qualitative tests were carried out as described by Taylor and Kent,¹⁰ and confirmed by emission spectra.¹¹

Estimation of (±)-2-Deoxy-2-fluoroglyceraldehyde.—Somogyi's cupric tartrate reagent¹² was found suitable for quantitative estimation of the fluoro-aldehyde in amounts between 0.63 and 33 mmoles. Provided that the reaction mixture was heated at 100° for 30 min., a reproducible linear calibration was obtained.

Oxidation of (±)-2-Deoxy-2-fluoroglyceraldehyde.—(i) *With bromine.* The fluoro-aldehyde (0.53 g., 5.5 mmoles) was dissolved in a solution of bromine (5.6 mmole) in water (30 ml.) and kept at room temperature for 24 hr.; a sample (freed from bromine by aeration) then reduced Fehling's solution only slightly. The excess of bromine was then removed and the solution was neutralised with silver carbonate, filtered, saturated with hydrogen sulphide, filtered again, and concentrated under reduced pressure to a colourless syrup (0.25 g.), which contained fluoride ion. Chromatography in propanol-ammonia revealed two anionic components, R_F 0.25 and 0.40 (cf. R_F 0.26 for fluoride and 0.51 for fluoroglycerate ion).

(ii) *With hypiodite.* The fluoro-aldehyde (0.36 g.) was dissolved in 55 ml. of a solution of 0.3N-iodine in N-barium iodide, and 0.4N-barium hydroxide (80 ml.) was added dropwise to the stirred mixture. After 20 min. 3N-sulphuric acid (12 ml.) and lead carbonate (12 g.) were added and the inorganic precipitate was removed.

The solution, when evaporated to dryness, yielded solid lead salts which did not reduce Fehling's solution or give a positive test for fluoride unless fused with potassium. Chromatography in propanol-ammonia revealed two anionic components, R_F 0.51 and 0.58 (cf. R_F 0.48 for glycerate ion, 0.59 for iodide).

Methyl (±)-2-Deoxy-2-fluoroglycerate [Methyl (±)-α-Fluoro-β-hydroxypropionate].—The dried impure lead salts described above were shaken with methanolic sulphuric acid (15 ml., 5% w/v), and the resulting inorganic precipitate was removed. A further 2.5 ml. of methanolic acid and 7.5 ml. of methanol were added, and the solution was refluxed for 7 hr. After neutralisation with lead carbonate, filtration, and evaporation, a fluorine-containing liquid (0.2 g., 15%) was obtained which was identified as *methyl (±)-2-deoxy-2-fluoroglycerate*, b. p. 18°/0.05 mm., n_D^{18} 1.4080 (Found: C, 38.9; H, 6.6; OMe, 25.3; F, 15.1. $C_4H_7O_3F$ requires C, 39.4; H, 5.7; OMe, 25.4; F, 15.6%). [Cf. methyl (±)-glycerate, b. p. 75°/0.15 mm., n_D^{19} 1.4450.]

(±)-2-Deoxy-2-fluoroglyceramide [(±)-α-Fluoro-β-hydroxypropionamide].—A methanolic solution (5 ml.) of the fluoro-ester (0.22 g.) was saturated with anhydrous ammonia at 0°. After 16 hr. at that temperature, the solvent was removed. The resulting *product*, recrystallised from dry acetone, had m. p. 115° (Found: C, 33.9; H, 5.6; N, 12.9; F, 17.0. $C_3H_5O_2NF$ required C, 33.7; H, 5.6; N, 13.1; F, 17.8%). A mixed m. p. with (±)-glyceramide (m. p. 90°) showed a depression.

(±)-2-Deoxy-2-fluoroglyceric Acid [(±)-α-Fluoro-β-hydroxypropionic Acid].—The lead salts (1.55 g.) of the fluoro-acid, obtained by oxidation of (±)-2-deoxy-2-fluoroglyceraldehyde (1 g.) by sodium hypiodite, were shaken with Dowex 50 (H^+) (5 g. of wet resin) in 20 ml. of water. Slow evaporation of the filtered solution at room temperature gave highly deliquescent crystals containing organically bound fluorine, which on titration had equiv. wt. 118 (Calc. for $C_3H_5O_3F$: equiv., 108). The substance was chromatographically homogenous (R_F 0.53 in propanol-ammonia).

Quinine Salts of 2-Deoxy-2-fluoroglyceric Acid.—The (±)-fluoro-acid, obtained by oxidation of 1 g. of the aldehyde, was neutralised with quinine (4.4 g.) at 100°. Excess of quinine was removed and the filtrate allowed to cool slowly to room temperature and then to 0°; an oil separated. The supernatant liquid was decanted and filtered. A white solid then separated which was recrystallised repeatedly from water, giving finally a crystalline quinine salt, m. p. 195—196°, $[\alpha]_D^{21}$ $-151^\circ \pm 2^\circ$ (*c* 2 in water) (Found: C, 61.5; H, 6.7; N, 6.8; F, 5.0. $C_{22}H_{29}O_5N_2F$ requires C, 64.0; H, 6.5; N, 6.5; F, 4.4%). The oil which first separated was very soluble in ethanol and with this solvent gave a crystalline product which after recrystallisation from water-ethanol (1 : 1 v/v) gave a quinine salt having m. p. 196°, $[\alpha]_D^{21}$ $-151^\circ \pm 2^\circ$ (*c* 2 in water).

The combined mother-liquors were evaporated under reduced pressure and dissolved in a dry ethanol (5 ml.). The solid, which separated, was recrystallised repeatedly from ethanol,

¹⁰ Taylor and Kent, *J.*, 1958, **168**, 872.

¹¹ Birks, *Spectrochim. Acta*, 1954, **6**, 169.

¹² Somogyi, *J. Biol. Chem.*, 1952, **195**, 19.

then having m. p. 179—180° and $[\alpha]_D^{20} - 132^\circ \pm 2^\circ$ (*c* 0.6 in water) (Found: C, 62.4; H, 6.8; N, 6.0; F, 4.8%).

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