671. *Organic Fluorine Compounds. Part XXII.* Fluorine Analogues of Mevalonic Acid.*

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γ-Fluoromevalonolactone has been synthetised, the essential step being condensation of fluoroacetone with formaldehyde at the methylene group; it powerfully inhibits the incorporation of acetate or mevalonate.

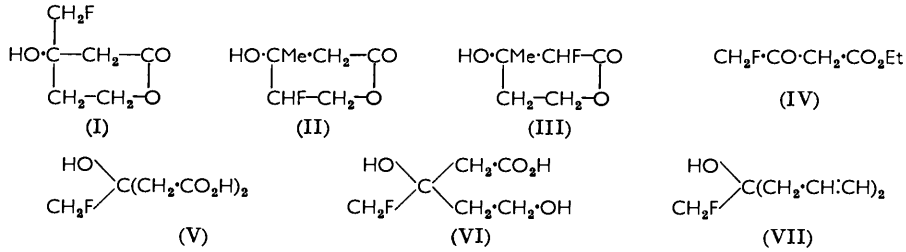
A synthesis of α-fluoromevalonolactone, based on the condensation of ethyl sodiofluoroacetate with 4-hydroxybutan-2-one or its acetate, gave only impure material owing to the ready dehydration.

The biosynthetic importance of mevalonic acid and the ability of fluorine to convert a metabolite into an antimetabolite made it interesting to study fluoromevalonolactones. Of the three structural isomers, (I) has been recently described [1] and studied.[2] The present paper describes some additional attempts at the oxidation of the intermediate (VII) and related reactions, but in the main it deals with the γ- (II) and the α-isomer (III). For the synthesis of (I) by application of the method of Folker *et al.*,[3] it was necessary to prepare 1-fluoro-4-hydroxybutan-2-one. The diethyl or ethylene ketal of the easily available [4] ethyl γ-fluoroacetoacetate (IV) was reduced with lithium aluminium hydride, but the product was very unstable and did not lend itself to further reaction. Since condensation of the ester (IV) with keten leads only to the corresponding enol acetate,[5] preparation of the acid (V) by oxidation of 4-fluoromethylhepta-1,6-dien-4-ol (VII) and its reduction to (VI) was attempted, but without success. Also, the acetate of this alcohol, obtained in 42% yield from ethyl fluoroacetate and allylmagnesium bromide, was unusually resistant to chromic acid in 80% acetic acid: the only product isolated contained two oxygen atoms more than the starting material and may have been the diepoxide.[5a]

* Part XXI, preceding paper.

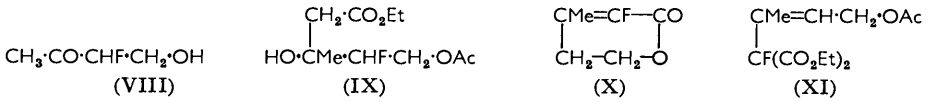
[1] Tschesche and Machleidt, *Annalen*, 1960, **631**, 61.
[2] Singer, Januszka, and Berman, *Proc. Soc. Exp. Biol. Med.*, 1959, **102**, 170.
[3] Hoffman *et al.*, *J. Amer. Chem. Soc.*, 1957, **79**, 2316.
[4] Bergmann, Cohen, and Shahak, *J.*, 1959, 3278.
[5] Bergmann, Cohen, Hoffman, and Meir-Rand, preceding paper.
[5a] Cf. Sankyo Co. Ltd., Jap. Pat. 3876; *Chem. Abs.*, 1961, **55**, 1452.

For the synthesis of compound (II), fluoroacetone was condensed with formaldehyde in the presence of sodium methoxide. In analogy to the behaviour of chloroacetone,[6] and in view of the stability of the product, it was probably 3-fluoro-4-hydroxybutan-2-one



(I) (II) (III) (IV) (V) (VI) (VII)

(VIII), and this was proved by a positive iodoform test. The derived acetate with zinc and ethyl bromoacetate gave ethyl 8-acetoxy-γ-fluoro-β-hydroxy-β-methylvalerate (IX), which was smoothly converted by alkali into the stable γ-fluoromevalonolactone (II). This product is liquid and appears to be sterically homogeneous; however, this point has not been established beyond doubt.



(VIII) (IX) (X) (XI)

It was expected that 3-oxobutyl acetate would react normally with ethyl chlorofluoroacetate in the same way as acetone [5] and ethyl methyl ketone.[7] However, with zinc or magnesium, either no reaction took place or untractable resins were obtained. Recourse was, therefore, had to the reaction [7] between the sodium derivative of the ethyl fluoroacetate and 4-hydroxybutan-2-one or its acetate. The infrared spectrum of the crude product corresponded to formula (III) which could have been formed directly in this reaction; however, upon distillation, water was split off and, after repeated distillation, the pure unsaturated lactone (X) was obtained. In the Reformatzky reaction between 3-oxobutyl acetate and diethyl bromofluoromalonate a product was formed which gave correct analyses for the unsaturated ester (XI). A boiling mixture of glacial acetic and hydrochloric acids cyclised this to the unsaturated lactone (X).

Dr. F. M. Singer [2] of the Squibb Institute, New Brunswick, N.J., has kindly compared the influence of the lactones (I) and (II) on the conversion of acetate and mevalonate, respectively, into cholesterol. The lactone (II) has a very strong inhibitory effect in both systems; in the acetate system, it is practically as active as lactone (I) (96% compared with 99% of inhibition), but in the mevalonate system less so (61%, compared with 88%).

A preliminary report on the synthetic experiments has been published.[8]

Experimental

Infrared data refer to liquid films.

3-Fluoro-4-hydroxybutan-2-one (VIII).—A stirred mixture of fluoroacetone (170 g.), paraformaldehyde (30 g.), and 2M-methanolic sodium methoxide (4 ml.) was heated on a water-bath for 5 min. Glacial acetic acid (1 ml.) was added, and the excess of fluoroacetone removed at 20 mm. and collected in a carbon dioxide–acetone trap. The recovered ketone was again treated as described above, the operation being carried out three times, in all. The product from these operations was combined and distilled, to yield the *hydroxy-ketone* (65 g., 42%), b. p.

[6] Buchman and Sargent, *J. Amer. Chem. Soc.*, 1945, **67**, 400; cf. the study by Bnkowska (*Roczniki Chem.*, 1958, **32**, 739; *Chem. Abs.*, 1959, **53**, 4117) of the preferred direction of the enolisation of chloroacetone.

[7] Bergmann and Cohen, *J.*, 1961, 3537.

[8] Bergmann and Cohen, *Tetrahedron Letters*, 1960, No. 8, 20.

57—58° (0·5 mm.), $\nu_{max.}$ 1724 (C=O, halogen-substituted [9]), 1100 and 1064 (C–F) cm.$^{-1}$ (Found: C, 45·8; H, 6·5; F, 18·2. $C_4H_7FO_2$ requires C, 45·3; H, 6·6; F, 17·9%).

The product (53 g.) was added, dropwise and with stirring, to acetic anhydride (60 g.) containing 5 drops of the boron trifluoride–ether complex at 30—35°. The mixture was stirred for 2 hr. at this temperature; then 2M-methanolic sodium methoxide (2 ml.) was added, and the mixture fractionated. The *acetate* (50 g., 68%) had b. p. 54—55°/0·4 mm., $\nu_{max.}$ 1724 (C=O), and (C–F) 1020, 1050, 1110 cm.$^{-1}$ (Found: C, 48·7; H, 6·3. $C_6H_9FO_3$ requires C, 48·6; H, 6·1%).

Ethyl δ-Acetoxy-γ-fluoro-β-methyl-β-hydroxyvalerate (IX).—A solution of the foregoing compound (50 g.) and ethyl bromoacetate (68 g.) in ether (350 ml.) was added, dropwise and with stirring, to activated zinc foil (26·5 g.) and the mixture refluxed until the zinc had reacted. After decomposition with sulphuric acid and crushed ice, separation of the ethereal layer, drying, and distillation gave the *ester* (45 g., 59%), b. p. 124—125°/0·4 mm., $\nu_{max.}$ 3400 (OH), 1740 (ester C=O), 1020, 1060, and 1090 (C–F) cm.$^{-1}$ (Found: C, 51·0; H, 7·4; F, 8·4. $C_{10}H_{17}FO_5$ requires C, 50·9; H, 7·2; F, 8·1%).

γ-Fluoromevalonolactone (II).—The foregoing ester (11·2 g.) in methanol (50 ml.) was treated at 0° with potassium hydroxide (5·6 g.) in methanol (30 ml.), then left at room temperature for 24 hr. Acetic acid was added to pH 5, and the mixture diluted with water (100 ml.) and extracted three times with ether. The aqueous phase was acidified with hydrochloric acid to pH 2—3 and extracted with ethyl acetate (3 × 50 ml.). The extracts were treated with charcoal and sodium sulphate, filtered, and distilled, to yield *γ-fluoromevalonolactone* (2 g., 27%), b. p. 124—125°/0·4 mm. (Found: C, 49·2; H, 6·3; F, 13·4. $C_6H_9FO_3$ requires C, 48·6; H, 6·1; F, 12·9%). The infrared spectrum showed the hydroxyl band at 3400 cm.$^{-1}$, in the C–F region bands at 1010, 1070, and 1100 cm.$^{-1}$, and the carbonyl band at 1720 cm.$^{-1}$ (somewhat low for a six-membered ring lactone).

α-Fluoromevalonolactone (III) *and 2-Fluoro-5-hydroxy-3-methylpent-2-enoic Acid Lactone* (X).—(*a*) Ethyl fluoroacetate (35 g.) in dry ether (100 ml.) was added to a stirred suspension of sodium hydride (8 g.) in dry ether (50 ml.) at 0—5° (the reaction was initiated by the addition of a few drops of ethanol). The mixture was stirred for 2 hr. at this temperature, then a solution of 3-oxobutyl acetate [3] (36 g.) in ether (50 ml.) was added dropwise, and the stirring continued for 3 hr. After decomposition with sulphuric acid and ice, separation of the organic material, and distillation, a mixture (9 g.) of α-fluoromevalonolactone (III) and its unsaturated analogue (X) was obtained. The infrared spectrum indicated the presence of a hydroxyl (3500 cm.$^{-1}$) and a C=O group (1625 cm.$^{-1}$); in the fluorine region, three frequencies were observed (1030, 1050, and 1100 cm.$^{-1}$). The carbonyl band was broad (centre at 1748 cm.$^{-1}$); it possibly represents the absorption both of the α-fluorinated saturated lactone-carbonyl, expected at 1745, and of the α-fluorinated αβ-unsaturated carbonyl, at 1754 cm.$^{-1}$ (see below).

On repeated distillation, the unsaturated *lactone* (X), b. p. 150—160°/0·5 mm., was obtained pure (Found: C, 55·8; H, 5·6; F, 14·3. $C_6H_7FO_2$ requires C, 55·4; H, 5·4; F, 14·6%), $\nu_{max.}$ 1660 and 1754 (C=O), 1025 and 1075 (C–F) cm.$^{-1}$.

(*b*) Ethyl fluoroacetate (106 g.) was added dropwise to a stirred suspension of sodium hydride (12 g.) in tetrahydrofuran [10] (300 ml.) at 0°. Stirring was continued until a clear brown solution had been formed; 3-oxobutyl acetate (51 g.) was then added dropwise, and the solution stirred for 4 hr., poured into an excess of ice-cold sulphuric acid, and extracted with ether. The ethereal extract was dried (Na_2SO_4) and distilled, to yield ethyl αγ-difluoroacetoacetate and a mixture (8 g.), b. p. 100—160°/0·5 mm. On redistillation, the product boiled at 120—125°/0·2 mm. and had n_D^{19} 1·4646 (Found: C, 51·2; H, 5·8; F, 13·7%).

(*c*) To the enol derivative of ethyl fluoroacetate (106 g.), prepared with sodium hydride (12 g.) in tetrahydrofuran (300 ml.), 4-hydroxybutan-2-one (44 g.) was added dropwise and with stirring at 0°. The solution was stirred at this temperature for 4 hr., left overnight, and worked up as above. Distillation gave material (15 g., 20%) boiling at 100—150°/0·5 mm. with much decomposition, and on redistillation gave material (10 g., 13·5%), b. p. 120—125°/0·2 mm., n_D^{19} 1·4623 (Found: C, 52·1; H, 6·1%).

Diethyl Bromofluoromalonate.—A stirred solution of diethyl fluoromalonate [11] (46 g.) in carbon tetrachloride (50 c.c.) was irradiated with ultraviolet light, while bromine (43 g.) was

[9] Cherrier, *Compt. rend.*, 1947, **225**, 997.
[10] Cf. Lawesson and Busch, *Acta Chem. Scand.*, 1959, **13**, 1717.
[11] Bergmann, Cohen, and Shahak, *J.*, 1959, 3286.

added dropwise. The reaction was very sluggish and required intermittent refluxing. When most of the bromine had reacted, the solution was cooled, washed with 5% sodium carbonate solution and water, dried (Na_2SO_4), and distilled. *Diethyl bromofluoromalonate* (43·5 g., 63%) boiled at 126—128°/27 mm. and had $\nu_{max.}$ 1763 (C=O, raised by halogen substitution [12]), 1045 and 1025 (C–F) cm.$^{-1}$ (Found: C, 32·8; H, 4·1. $C_7H_{10}BrFO_4$ requires C, 32·7; H, 3·9%).

Diethyl 4-Acetoxy-1-fluoro-2-methylbut-2-ene-1,1-dicarboxylate (XI).—A solution of diethyl bromofluoromalonate (35 g.) and 3-oxobutyl acetate (18 g.) in anhydrous ether (100 ml.) was added, dropwise and with stirring, to clean zinc foil (10 g.). The mixture was refluxed for 5 hr., then poured on ice and an excess of sulphuric acid; the ethereal solution was separated, dried, and distilled. The fraction of b. p. 100—150°/0·5 mm. (15 g., 37%) was redistilled, to yield the *ester* (XI), b. p. 120—121°/0·5 mm., $\nu_{max.}$ 1754 (C=O, raised by halogen substitution [12]), shoulder at 1725 (ester C=O), 1690 (C=O double bond), 1100 and 1030 (C–F) cm.$^{-1}$ (Found: C, 53·2; H, 6·7. $C_{13}H_{19}FO_6$ requires C, 53·7; H, 6·6%).

2-Fluoro-5-hydroxy-3-methylpent-2-enoic Acid Lactone (X).—The foregoing compound (5 g.) was heated on a water-bath with acetic acid (10 ml.) and hydrochloric acid (10 ml.) for 30 min. Distillation gave the unsaturated lactone (X), b. p. 150—160°/0·5 mm. (Found: C, 54·5; H, 5·8. Calc. for $C_6H_7FO_2$: C, 55·4; H, 5·4%). The infrared spectrum was identical with that of the compound prepared by the alternative method.

4-Fluoromethylhepta-1,6-dien-4-ol (VII).—To a Grignard solution [from magnesium (24 g.) and allyl bromide (60·5 g.) in ether (300 ml.)], ethyl fluoroacetate (26·5 g.) in ether (100 ml.) was added dropwise and with stirring at −20°. Vigorous stirring was maintained at this temperature for 2 hr., then the mixture was poured on ice and sulphuric acid. The ethereal solution was separated, dried (Na_2SO_4), and distilled. The alcohol (15 g., 42%) had b. p. 72—73°/20 mm., (lit.,[1] 59°/12 mm.), $\nu_{max.}$ 3420 (OH), 1650 (C=C), 1010 (C–F) cm.$^{-1}$ (Found: C, 67·1; H, 9·1; F, 12·6. $C_8H_{13}FO$ requires C, 66·7; H, 9·0; F, 13·2%).

The boron trifluoride–ether complex (3 drops) was added cautiously to a mixture of the alcohol (14 g.) and acetic anhydride (12 g.). When the reaction subsided, the mixture was heated on a water-bath for 1 hr. and distilled. The *acetate* (16 g., 85%) boiled at 86—87°/20 mm. and had $\nu_{max.}$ 1740 (C=O), 1650 (C=C), 1020 (C–F) cm.$^{-1}$ (Found: C, 64·6; H, 8·2; F, 10·0. $C_{10}H_{15}FO_2$ requires C, 64·5; H, 8·1; F, 10·2%).

4-Acetoxy-1,2:6,7-diepoxy-4-fluoromethylheptane (?).—The preceding compound (14 g.) was dissolved in acetic acid (80 ml.) and water (20 ml.), and chromic anhydride (25 g.) added in small portions and with stirring at 20—25°. The mixture was stirred for 12 hr. at room temperature, diluted with water, and extracted repeatedly with ether. Distillation of the extract gave unchanged acetate (3 g.) and the (?) diepoxide (2 g.), b. p. 114—116°/0·5 mm., which was insoluble in water, soluble in all organic solvents. $\nu_{max.}$ 1728 (C=O), 1030 (C–F), 1250 and 930 (epoxide [13]) cm.$^{-1}$ (Found: C, 54·2; H, 6·5. Calc. for $C_{10}H_{15}FO_4$: C, 55·0; H, 6·9%).

Ethyl ββ-Diethoxy-γ-fluorobutyrate.—A mixture of ethyl γ-fluoroacetoacetate [4] (71 g.), ethyl orthoformate (142 g.), and boron trifluoride–ether complex (2 ml.) was kept for 48 hr. at room temperature, potassium hydroxide (4 g.) in a little methanol added, and the mixture fractionated. The *ketal* produced (70 g., 66%) boiled at 63—65°/0·5 mm. (Found: C, 54·2; H, 8·6. $C_{10}H_{19}FO_4$ requires C, 54·1; H, 8·6%).

Ethyl (2-Fluoromethyl-1,3-dioxolan-2-yl)acetate.—Ethyl γ-fluoroacetoacetate (10 g.) was azeotropically distilled with ethylene glycol (4 g.), benzene (50 ml.), and a trace of toluene-*p*-sulphonic acid. Then solid calcium carbonate was added and the filtered solution distilled. The *ketal* boiled at 104—106°/18 mm. (Found: C, 49·7; H, 6·7; F, 10·4. $C_8H_{13}FO_4$ requires C, 50·0; H, 6·7; F, 10·0%).

Ethyl α-fluoro-α-(2-methyl-1,3-dioxolan-2-yl)acetate, prepared analogously, had b. p. 100—101°/18 mm. (Found: C, 50·0; H, 6·9; F, 10·0%).

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