[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. XV.[1] Some ω-Fluoro-β-Ketoesters and ω-Fluoroketones

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The preparation of representative ω-fluoro-β-ketoesters and ω-fluoroketones is reported. The toxicological properties of the former are consistent with the theory that β-ketoacids are intermediary metabolites of the corresponding fatty acids. The toxicological properties of the latter are discussed in terms of ω-oxidation and of oxidative cleavage.

In accordance with the β-oxidation theory, ketoacids are formed as intermediates in the metabolism of fatty acids, activation for the degradations being effected by the initial formation of the thiol-ester of coenzyme A. It was of interest, therefore, as an extension of our researches into the preparation and toxicological properties of ω-fluorocarboxylic esters and acids,[2,3] to prepare representative members of ω-fluoro-3-oxocarboxylates, $F(CH_2)_nCOCH_2COOR$ and ω-fluoroalkyl ketones, $F(CH_2)_nCOR$, in order to compare their toxicities with those of the corresponding ω-fluoroacids. The members prepared are listed in Table I.

The ω-fluoro-β-ketoesters were obtained readily from ω-fluorocarboxylic acid chlorides[4] by the method of Bowman and Fordham.[5] This involved the reaction of ethyl tetrahydropyranyl sodiomalonate with the appropriate acid chloride, followed by removal of the tetrahydropyranyl group and decarboxylation

$$F(CH_2)_nCOCl + NaCH(COOEt)COOC_5H_9O \longrightarrow F(CH_2)_nCOCH(COOEt)COOC_5H_9O \longrightarrow F(CH_2)_nCOCH(COOEt)COOH \longrightarrow F(CH_2)_nCOCH_2COOEt \quad (I)$$

Ethyl ω-fluoroacetoacetate[6] (I, $n = 1$) proved to be difficult to purify. Two methods were successfully employed: formation and purification of the Girard P derivative with subsequent regeneration and distillation of the ketoester, and re-esterification[7] of the crude ketoester prior to distillation. When the latter method was applied to crude ethyl 8-fluoro-3-oxoöctanoate (I, $n = 5$), cleavage occurred forming ethyl 6-fluorohexanoate in 57% yield. Caution is therefore necessary in selecting the method of purification.

Fluoromethyl ketones were prepared from acyl chlorides by conversion to the diazomethyl ketones, followed by treatment with anhydrous hydrogen fluoride

$$RCOCl \longrightarrow RCOCHN_2 \xrightarrow{HF} RCOCH_2F + N_2$$

This method affords a convenient route to compounds containing the FCH_2CO- grouping. Since the completion of this work, a similar method employing acyl fluorides has been published by Olah and Kuhn.[8]

The other mono- and difluorinated aliphatic ketones listed in Table I were prepared by Grignard reactions[9] of ω-fluoroalkyl chlorides[10] with the appropriate acid chlorides or anhydrides. The ω-fluoroalkyl phenyl ketones were obtained from benzonitrile by reaction either with ω-fluoroalkyllithium compounds or with ω-fluoroalkylmagnesium halides. The preparative details of this work are being described in a separate series of papers.[11]

TABLE I

TOXICITY OF SOME ω-FLUORO-β-KETOESTERS AND ω-FLUOROKETONES

Compound	Formula	L.D. 50 for mice (intraperitoneal), mg./kg.
Ethyl ω-fluoroacetoacetate	FCH_2COCH_2COOEt	*ca.* 2.5[a]
Ethyl 8-fluoro-3-oxoöctanoate	$F(CH_2)_5COCH_2COOEt$	1.3
Ethyl 9-fluoro-3-oxononanoate	$F(CH_2)_6COCH_2COOEt$	67
Ethyl 12-fluoro-3-oxododecanoate	$F(CH_2)_9COCH_2COOEt$	1.95
1-Fluoro-2-heptanone[b]	$FCH_2CO(CH_2)_4CH_3$	60
1-Fluoro-2-octanone	$FCH_2CO(CH_2)_5CH_3$	8–10
1-Fluoro-2-decanone	$FCH_2CO(CH_2)_7CH_3$	7.5
1,7-Difluoro-2-heptanone	$FCH_2CO(CH_2)_4F$	0.68
8-Fluoro-2-octanone	$F(CH_2)_6COCH_3$	3
9-Fluoro-2-nonanone	$F(CH_2)_7COCH_3$	16
10-Fluoro-2-decanone	$F(CH_2)_8COCH_3$	1.2
11-Fluoro-2-undecanone	$F(CH_2)_9COCH_3$	11.8
12-Fluoro-2-dodecanone	$F(CH_2)_{10}COCH_3$	1.5
12-Fluoro-6-dodecanone	$F(CH_2)_6CO(CH_2)_4CH_3$	4.5
1,12-Difluoro-6-dodecanone	$F(CH_2)_6CO(CH_2)_5F$	2.2[c]
1,13-Difluoro-7-tridecanone	$F(CH_2)_6CO(CH_2)_6F$	9.6
1,19-Difluoro-10-nonadecanone[d]	$F(CH_2)_9CO(CH_2)_9F$	*ca.* 40[e]
6-Fluorohexyl phenyl ketone	$F(CH_2)_6COC_6H_5$	>100
8-Fluoroöctyl phenyl ketone	$F(CH_2)_8COC_6H_5$	*ca.* 100
9-Fluorononyl phenyl ketone	$F(CH_2)_9COC_6H_5$	*ca.* 90

[a] The solvent (propylene glycol) appeared to be giving rise to some synergistic effect. With no solvent, a dose of 6.5 mg./kg. caused $^5/_{10}$ deaths, whereas in propylene glycol, the apparent L.D. 50 by intraperitoneal injection was *ca.* 0.4 mg./kg. On further examination, wide variation was observed. The figure listed (2.5 mg./kg.)[6] is a weighted average of the various results. [b] The simplest member of the series, monofluoroacetone, FCH_2COCH_3 has been reported[12] to be non-toxic to rats at a dose of 10 mg./kg. [c] A by-product[11] in the synthesis, 5-fluoroamyl-bis-(6-fluorohexyl)-carbinol, $F(CH_2)_5C(OH)[(CH_2)_6F]_2$, had L.D. 50, 2.2 mg./kg. [d] Obtained as by-product[11] in the reaction of 9-fluorononylmagnesium chloride with ethyl chloroformate. The low toxicity may be associated with the low solubility of this ketone in propylene glycol.

(1) (a) Issued as DRB Report No. SW-33; (b) Part XIV, THIS JOURNAL, **79**, 1956 (1957).

(2) F. J. Buckle, F. L. M. Pattison and B. C. Saunders, *J. Chem. Soc.*, 1471 (1949).

(3) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1956).

(4) F. L. M. Pattison, R. R. Fraser, G. J. O'Neill and J. F. K. Wilshire, *ibid.*, **21**, 887 (1956).

(5) R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 3945 (1952).

(6) R. R. Fraser and F. L. M. Pattison, *Nature*, **176**, 696 (1955).

(7) B. R. Baker, M. V. Querry, S. R. Safir and S. Bernstein, *J. Org. Chem.*, **12**, 138 (1947).

(8) G. Olah and S. Kuhn, *Chem. Ber.*, **89**, 864 (1956); see also I. L. Knunyants, Ya. M. Kisel' and E. G. Bykhovskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 377 (1956).

(9) W. C. Howell and F. L. M. Pattison, *Chemistry & Industry*, 949 (1955).

(10) F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 748 (1956).

(11) F. L. M. Pattison and W. C. Howell, *ibid.*, **21**, 879 (1956), and subsequent papers in the series.

(12) S. Gitter, I. Blank and E. D. Bergmann, *Koninkl. Ned. Akad. Wetenschap. Proc.*, Series C, **56**, 427 (1953).

The toxicities of the four ω-fluoro-3-oxocarboxylates listed in Table I are paralleled by those of the corresponding ω-fluorocarboxylates,[3] thus establishing the biochemical similarity of the two classes. This is consistent with the theory that β-ketoacids are intermediary metabolites of fatty acids[13]; by extending the conclusions to unfluorinated members, these results afford independent evidence for the mode of breakdown of fatty acids *in vivo*.

The toxicities of the three fluoromethyl alkyl ketones indicate that ω-oxidation may play a significant role in their metabolism. Thus, 1-fluoro-2-heptanone would give rise to the fluoroketoacid $FCH_2CO(CH_2)_4COOH$, which in turn would form the relatively non-toxic fluoropyruvic acid[14] by β-oxidation. On the other hand, the two toxic members by the same mechanism would form the toxic ω-fluoroacetoacetic acid. It is possible that direct oxidative cleavage may also occur to a small extent, forming fluoroacetic acid in each instance; this would provide a partial explanation for the unexpectedly high toxicity of 1,7-difluoro-2-heptanone, which presumably could give rise also to 6-fluorohexanoic acid. Further evidence for ω-oxidation recently has been obtained here in the study of *n*-alkyl fluorides, of which the even members have been shown to be much more toxic than the odd members; details of this work will be described in a later paper.

When considering the compounds of the general formula $F(CH_2)_nCOCH_3$, it is evident that the members for which *n* is even are relatively more toxic than those for which *n* is odd. However, those compounds in which *n* is odd, although less active, still exhibit toxicities comparable to those of fluoroacetic acid. These facts may be explained by considering two competing modes of breakdown

$$F(CH_2)_nCOCH_3 \longrightarrow F(CH_2)_nCOOH + HCOOH$$

$$F(CH_2)_nCOCH_3 \longrightarrow F(CH_2)_{n-1}COOH + CH_3COOH$$

From the toxicity data obtained, the first of these is subordinate to the second, although both apparently occur to an appreciable extent. This general trend therefore conforms to the Popoff rule regarding the chemical oxidation of ketones, which states that the carbonyl group normally goes with the smaller radical to a greater extent than with the larger radical. Both the odd and even members gave rise to citric acid accumulation, but the effect (on a molar basis) was greater with the even members, as was expected from the above discussion.

Within the limits of biological variation, the toxicities of 12-fluoro-6-dodecanone, 1,12-difluoro-6-dodecanone and 1,13-difluoro-7-tridecanone appear to confirm the above implication that the predominant metabolic fragments may be predicted correctly by the Popoff rule. Further evidence is supplied by the marked similarity in toxicity of 12-fluoro-6-dodecanone and of 8-fluoro-2-octanone on a molar basis.

The ω-fluoroalkyl phenyl ketones are all relatively non-toxic, possibly due to suppression of the oxidative mechanisms by the phenyl group; these results are in agreement with the low toxicity of the lowest member of the series, ω-fluoroacetophenone, the minimum lethal dose of which has been reported[15] to be 225 mg./kg. for rats and mice.

The above arguments are based solely on simple toxicity determinations; the conclusions are therefore tentative, and subject to confirmation by more specific procedures.

Experimental[16]

Ethyl ω-Fluoroacetoacetate.—Ethyl hydrogen malonate[17] (13.2 g., 0.1 mole) was added with stirring, over a 2-hour period, to a solution of dihydropyran (12.6 g., 0.15 mole) in benzene (100 ml.) acidified with two drops of concd. sulfuric acid. The temperature of the mixture was maintained at less than 30° by means of an ice-bath. Stirring was continued for a further 30 minutes after the addition was complete. Traces of free acid were removed by stirring the mixture in the presence of solid potassium hydroxide (8 g.) for 30 minutes, and the solution was then decanted from the solid material. Benzene and excess dihydropyran were removed by distillation under reduced pressure, using a water-bath maintained at less than 30°. The residual ester in benzene (100 ml.) was added to a 50% sodium dispersion[18] (containing 2.3 g. of sodium, 0.1 mole, dispersed in toluene) diluted with anhydrous benzene (200 ml.), at a temperature of less than 35°. When dissolution of the metal was complete, a solution of fluoroacetyl chloride[19] (9.65 g., 0.1 mole) in benzene (100 ml.) was added and the mixture was allowed to stand overnight. After removal of the resultant gel by filtration, acetic acid (10 ml.) and *p*-toluenesulfonic acid (0.5 g.) were added to the solution, and the mixture was heated under reflux until evolution of carbon dioxide ceased (*ca.* two hours). The cooled mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, giving crude ethyl ω-fluoroacetoacetate as the residue (10 g.).

Direct distillation of the residue under reduced pressure gave a low yield of impure ester. It is therefore recommended that either of the following procedures be carried out prior to the final distillation; the second of these was found to be the more satisfactory. (a) A mixture of the residue, absolute ethanol (160 ml.), glacial acetic acid (15.5 ml.) and Girard P reagent (16 g.) was heated under reflux for one hour.[20] After cooling, the solution was poured into ice-water (1750 ml.) containing sodium carbonate monohydrate (13.25 g.), sufficient to neutralize 90% of the acetic acid. The *p*H was checked with brom thymol blue. After thorough extraction with ether, the aqueous portion was made 0.5 *N* using hydrochloric acid, and was allowed to stand for one hour with occasional stirring. It was then saturated with sodium chloride and thoroughly extracted with ether. The extracts were washed with 5% sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the ether and distillation of the residue gave pure ethyl ω-fluoroacetoacetate. (b) The residue was placed in a flask containing absolute ethanol (50 ml.), benzene (75 ml.) and concd. sulfuric acid (5 ml.). The mixture was heated under reflux for 16 hours under a Soxhlet extractor containing anhydrous magnesium sulfate (25 g.) in the thimble.[7] The mixture was cooled, washed with water and separated. After removal of the solvent and residual water under reduced pressure, distillation of the dark residue gave ethyl ω-fluoroacetoacetate as a colorless liquid with an odor almost indistinguishable from that of ethyl acetoacetate; yield 5.15 g. (35%), b.p. 78–80° (12 mm.), $n^{25}D$ 1.4180.

(13) See for example, I. L. Chaikoff and G. W. Brown, Jr., in "Chemical Pathways of Metabolism," (D. M. Greenberg, editor, Academic Press, Inc., New York, N. Y., 1954, p. 277.

(14) I. Blank, J. Mager and E. D. Bergmann, *J. Chem. Soc.*, 2190 (1955).

(15) F. Bergmann and A. Kalmus, THIS JOURNAL, **76**, 4137 (1954).

(16) (a) The microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; (b) melting points and boiling points are uncorrected.

(17) D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944).

(18) Kindly supplied by National Distillers Chemical Corporation.

(19) F. L. M. Pattison, R. R. Fraser, E. J. Middleton, J. C. Schneider and J. B. Stothers, *Can. J. Technol.*, **34**, 21 (1956).

(20) A. Petit and S. Tallard, *Industrie parfum.*, **3**, 75 (1948).

Anal. Calcd. for $C_6H_9FO_3$: C, 48.65; H, 6.08. Found: C, 48.64; H, 6.26.

2,4-Dinitrophenylhydrazone, yellow crystals from methanol, m.p. 91–91.5°. *Anal.* Calcd. for $C_{12}H_{13}FN_4O_6$: C, 43.90; H, 3.99; N, 17.07. Found: C, 43.71; H, 4.16; N, 17.19.

Ethyl 8-fluoro-3-oxoöctanoate was prepared from 6-fluorohexanoyl chloride[4] (7.6 g., 0.05 mole) in the same way. Distillation of the residue after solvent removal gave the ester, b.p. 106–114° (2–3 mm.). This was purified by being dissolved in petroleum ether and washed once with 10% sodium bicarbonate (10 ml.). This volume of sodium bicarbonate should not be exceeded, since the water-soluble sodium salt of the enol form of the ketoester is readily formed and remains in the aqueous phase. After washing with water, ethylene chloride was added to the organic layer, and the solvents were removed under reduced pressure. The residue on fractionation yielded ethyl 8-fluoro-3-oxoöctanoate (5 g., 49%) of b.p. 107° (3 mm.) and $n^{25}D$ 1.4223.

Anal. Calcd. for $C_{10}H_{17}FO_3$: C, 58.83; H, 8.33. Found: C, 58.75; H, 8.32.

When the esterification method of purification was carried out (see above), **ethyl 6-fluorohexanoate** (9.2 g., 57%) was obtained, b.p. 80–83° (10 mm.), $n^{25}D$ 1.4072 [Buckle, *et al.*,[2] report b.p. 82–84° (14 mm.)].

Anal. Calcd. for $C_8H_{15}FO_2$: C, 59.27; H, 9.26. Found: C, 59.11; H, 9.16.

Ethyl 9-fluoro-3-oxononanoate was prepared from 7-fluoroheptanoyl chloride[4] (8.3 g., 0.05 mole) in the same way. Distillation of the residue after solvent removal gave the ester, b.p. 115–118° (1.3 mm.). This was purified by being dissolved in petroleum ether and washed with 10% sodium bicarbonate (10 ml.) and with water. Ethylene chloride was added to the petroleum ether solution, and the solvents were removed under reduced pressure. The residue on fractionation yielded ethyl 9-fluoro-3-oxononanoate (4.7 g., 43%) of b.p. 122° (1.7 mm.) and $n^{25}D$ 1.4247.

Anal. Calcd. for $C_{11}H_{19}FO_3$: C, 60.54; H, 8.72. Found: C, 60.45; H, 8.70.

Ethyl 12-fluoro-3-oxododecanoate was prepared from 10-fluorodecanoyl chloride[4] (10.4 g., 0.05 mole) in the same way. Distillation of the residue after solvent removal gave the ester, b.p. 141–144° (2 mm.). This was recrystallized several times from petroleum ether, yielding pure ethyl 12-fluoro-3-oxododecanoate (5.9 g., 42%), m.p. 47–47.5°.

Anal. Calcd. for $C_{14}H_{25}FO_3$: C, 64.59; H, 9.68. Found: C, 64.32; H, 9.91.

The phenyl pyrazolone derivative, colorless crystals from methanol, m.p. 96–96.5°. *Anal.* Calcd. for $C_{18}H_{25}FN_2O$: N, 9.21. Found: N, 9.31.

1-Fluoro-2-heptanone.—Hexanoyl chloride (8.0 g., 0.06 mole) was added to a well-stirred ethereal solution of diazomethane (12.6 g., 0.3 mole), cooled in an ice-bath. Stirring was continued for two hours, and the ether was then removed. The residue (12 g.) in ether (40 ml.) was slowly added to liquid anhydrous hydrogen fluoride (5 g.) in a polyethylene flask immersed in a Dry Ice–acetone-bath. The mixture was allowed to warm slowly to room temperature overnight, and then was poured over anhydrous potassium fluoride (20 g.). The liquid was decanted, the solid cake was washed with dry ether, and the combined ethereal solutions were dried over anhydrous potassium fluoride. After removal of the ether, the residue on fractionation gave 1-fluoro-2-heptanone (3.0 g., 38%) of b.p. 54° (13 mm.) and $n^{25}D$ 1.4048.

Anal. Calcd. for $C_7H_{13}FO$: C, 63.60; H, 9.91. Found: C, 63.83; H, 9.81.

1-Fluoro-2-octanone was prepared similarly from heptanoyl chloride in 23% yield, b.p. 70° (11 mm.) and $n^{25}D$ 1.4112. *Anal.* Calcd. for $C_8H_{15}FO$: C, 65.71; H, 10.34. Found: C, 65.82; H, 10.48.

1-Fluoro-2-decanone was prepared similarly from nonanoyl chloride in 40% yield, b.p. 99° (11.5 mm.) and $n^{25}D$ 1.4205. *Anal.* Calcd. for $C_{10}H_{19}FO$: C, 68.91; H, 11.00. Found: C, 68.83; H, 11.02.

1,7-Difluoro-2-heptanone was prepared similarly from 6-fluorohexanoyl chloride[4] in 60% yield, b.p. 102–104° (42 mm.) and $n^{25}D$ 1.4115. *Anal.* Calcd. for $C_7H_{12}F_2O$: C, 55.98; H, 8.06. Found: C, 55.88; H, 7.87.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN COMPANY, DIVISION OF EASTMAN KODAK COMPANY]

Preparation and Properties of Diethyl Acetoxyalkylphosphonates

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Diethyl 1-acetoxyalkylphosphonates were prepared from diethyl 1-hydroxyalkylphosphonates and ketene in good yields. The infrared spectrum of diethyl 1-acetoxyethylphosphonate was compared with that of the product of the reaction of vinyl acetate and diethyl hydrogen phosphite in the presence of sodium ethoxide. It was thus shown that the reaction product is diethyl 1-acetoxyethylphosphonate rather than diethyl 2-acetoxyethylphosphonate. For comparison, diethyl 2-acetoxyethylphosphonate was prepared by the Arbuzov reaction of 2-bromoethyl acetate and triethyl phosphite. The addition of diethyl hydrogen phosphite to vinyl acetate in the presence of benzoyl peroxide also gave diethyl 2-acetoxyethylphosphonate. The infrared spectra of the two products were identical.

In 1952, Pudovik reported that dialkyl hydrogen phosphites react with vinyl acetate to produce dialkyl 2-acetoxyethylphosphonates according to the equation[1]

$$CH_3COOCH{=}CH_2 + HP(O)(OR)_2 \xrightarrow{NaOR} CH_3COOCH_2CH_2P(O)(OR)_2 \quad (1)$$

Pudovik gave no real proof of structure, stating only that saponification of the reaction product from diethyl hydrogen phosphite and vinyl acetate

(1) A. N. Pudovik, *J. Gen. Chem. (U.S.S.R.)*, Consultants Bureau English Translation, **22**, 537 (1952).