[Contribution from the Department of Chemistry, University of Western Ontario]

Toxic Fluorine Compounds. IX.[1] ω-Fluorocarboxylic Esters and Acids

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Members of the series of ω-fluorocarboxylic esters and acids were synthesized, and their properties were determined. Toxicological results were found to be consistent with previously reported observations.

Several members of the series of ω-fluorocarboxylic esters, $F(CH_2)_nCOOR$ ($n = 1,2,3,4,5,7,9,10,11$) have been described,[2] and their toxicological properties have been correlated with chemical structure.[2,3] In this communication are described the members ($n = 6, 8$) missing from the above series, and certain higher members.[4] Alternative and improved methods have been developed for preparing the ω-fluorocarboxylate esters, and the results are summarized in Table I.

ω-Fluorocarboxylic acids were prepared in order to compare their toxicity with that of the corresponding esters; many of the acids were also required as intermediates for other work. Several methods of preparation were developed, and the results are summarized in Table II.

Care is necessary in preparing 4-fluorobutyric and 5-fluorovaleric acids, since both show a marked tendency to form the corresponding lactones by loss of hydrogen fluoride. For example, in an attempted hydrolysis of 5-fluorovaleronitrile with concentrated hydrochloric acid, 5-chlorovaleric acid was formed in 52% yield; this is readily explained by the intermediate 5-fluorovaleric acid forming valerolactone, which in turn is cleaved by the hydrochloric acid.

Toxicological results are listed in Table III. In general, the acids are more toxic than the corresponding esters, and the figures for both series conform to the toxicity pattern previously described.[2,3,4,11] The pronounced difference in toxicity between 18-fluorostearic acid, $F(CH_2)_{17}COOH$ and 9(10)-fluorostearic acid,[6] $CH_3(CH_2)_nCHF(CH_2)_mCOOH$ ($n = 7$ or 8; $m = 8$ or 7) emphasizes the high specificity of the ω-fluorine atom for pharmacological activity. The unsaturated ω-fluorocarboxylates (C_4, C_{12}, C_{13}) have toxicities very similar to those of the corresponding saturated members; this fact is consistent with modern concepts of fatty acid metabolism.

TABLE III

Toxicity[a] of ω-Fluorocarboxylic Esters and Acids

	L.D. 50 for mice (intraperitoneal), mg./kg.	
ω-Fluorocarboxylate	$R = C_2H_5$	$R = H$
FCH_2COOR[b]	7.5[c]	6.6
$F(CH_2)_2COOR$	—	60
$F(CH_2)_3COOR$	0.7[c]	0.65[d]
$FCH_2CH{:}CHCOOR$	1.25	—
$F(CH_2)_4COOR$	>100[c]	>100
$F(CH_2)_5COOR$	1.61[c]	1.35
$F(CH_2)_6COOR$	>100[c]	40
$F(CH_2)_7COOR$	1.75	0.64
$F(CH_2)_8COOR$	70	>100
$F(CH_2)_9COOR$	1.65	1.5[d,e]
$F(CH_2)_{10}COOR$	>100	57.5
$F(CH_2)_{11}COOR$	—	1.25
$F(CH_2)_9CH{:}CHCOOR$	—	1.55
$F(CH_2)_{10}CH{:}CHCOOR$	—	72
$F(CH_2)_{15}COOR$	7	—
$F(CH_2)_{17}COOR$	18[c]	5.7[f]

[a] Esters and acids were administered in propylene glycol, and sodium salts in water. Results using the two solvents are apparently similar, as is indicated by the values for methyl fluoroacetate in water (8.2 mg./kg.) and in propylene glycol (7.5 mg./kg.). [b] Methyl fluoroacetate was taken as a standard for comparison. [c] Methyl ester. [d] Sodium salt. The toxicity of the free acids and of the sodium salts are very similar, as is shown by the L.D. 50 of sodium 10-fluorodecanoate (1.5 mg./kg.) and of 10-fluorodecanoic acid (1.5 mg./kg.). [e] For comparison, 10-chlorodecanoic acid has L.D. 50, 68.8 mg./kg. [f] For comparison, 9(10)-fluorostearic acid has L.D. 50, >400 mg./kg.

EXPERIMENTAL[16]

INTERMEDIATES

ω-Fluoroalcohols[11] and *ω-fluoronitriles*[17] have been described elsewhere.

Ethyl 7-bromoheptanoate was prepared from tetrahydropyran, as described by Ames, Bowman, and Mason,[18] b.p. 112°/5 mm.

Ethyl 9-bromononanoate was prepared by two methods: (a) from sebacic acid by half-esterification,[11,19] conversion to the silver salt, and finally degradation with bromine in

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(1) Issued as DRB Report No. SW-27. Part VIII. *J. Am. Chem. Soc.*, **78**, 3846 (1956).

(2) Buckle, Pattison, and Saunders, *J. Chem. Soc.*, 1471 (1949).

(3) Pattison and Saunders, *J. Chem. Soc.*, 2745 (1949).

(4) Pattison, *Nature*, **172**, 1139 (1953).

(16) (a) All melting points and boiling points are uncorrected; (b) Physical constants and analytical results are listed in Tables I and II.

(17) Pattison, Cott, Howell, and White, *J. Am. Chem. Soc.*, **78**, 3484 (1956).

(18) Ames, Bowman, and Mason, *J. Chem. Soc.*, 174 (1950).

(19) Swann, Oehler, and Buswell, *Org. Syntheses*, Coll. Vol. **2**, 276 (1943).

TABLE I

ω-FLUOROCARBOXYLIC ESTERS, PREPARATION, PHYSICAL CONSTANTS, AND ANALYTICAL DATA

Compound	Formula	Method of Preparation[a]	Yield, %	B.P.		n_D^{25}	Analyses C		H		F	
				°C.	Mm.		Calc'd	Found	Calc'd	Found	Calc'd	Found
Methyl fluoroacetate[b]	FCH_2COOCH_3	1	99	103–105	756	1.3659						
Ethyl fluoroacetate[c]	$FCH_2COOC_2H_5$	2	90	114–118		1.3740						
		3	47	115–117	740	1.3750						
Methyl 3-fluoropropionate[d]	$F(CH_2)_2COOCH_3$	4	86	118–120		1.3779						
Ethyl 4-fluorocrotonate	$FCH_2CH:CHCOOC_2H_5$	3	50	53.5–54	11	1.4180	54.54	54.44	6.82	6.66		
Methyl 5-fluorovalerate	$F(CH_2)_4COOCH_3$	6	83.5	72–74	25	1.3973	53.70	53.68	8.26	7.90		
Methyl 6-fluorohexanoate	$F(CH_2)_5COOCH_3$	6	71.5	70–71	9	1.4045	56.72	56.58	8.84	8.66		
Methyl 7-fluoroheptanoate	$F(CH_2)_6COOCH_3$	4	88	92–93	13	1.4101	59.27	59.16	9.26	9.26		
Ethyl 7-fluoroheptanoate	$F(CH_2)_6COOC_2H_5$	5	40.3	39–40	0.1		61.34	61.32	9.72	9.52	10.78	10.6
		7	34	63–64	1							
		8	48	97–97.5	11	1.4111						
Ethyl 8-fluoroöctanoate[e]	$F(CH_2)_7COOC_2H_5$	8	49	106.5–107	9	1.4158	63.13	63.08	10.07	9.72		
Ethyl 9-fluorononanoate	$F(CH_2)_8COOC_2H_5$	7	35	87–88	1		64.67	64.42	10.36	10.16	9.14	8.7
		8	54.5	120–120.5	9	1.4191						
Ethyl 10-fluorodecanoate[f]	$F(CH_2)_9COOC_2H_5$	8	61	136–136.5	11	1.4228	66.02	65.62	10.62	10.32		
Ethyl 11-fluoroundecanoate[g]	$F(CH_2)_{10}COOC_2H_5$	5[h]	26	145–146	9	1.4257	67.20	67.19	10.85	10.74	8.19	8.0
		8	54	145–146	9	1.4257						
Ethyl 16-fluorohexadecanoate	$F(CH_2)_{15}COOC_2H_5$	7[i]	20	175–180[j]	0.9		71.54	71.92	11.59	11.60		
Methyl 18-fluoroöctadecanoate[k]	$F(CH_2)_{17}COOCH_3$	9	4.8	143–148	0.6	m.p. 33–34°	72.14	72.25	11.70	11.48		

[a] Methods of preparation: 1, sodium salt + dimethyl sulfate; 2, sodium salt + diethyl sulfate; 3, mesyloxy ester + potassium fluoride;[5] 4, esterification of acid with appropriate alcohol; 5, bromoester + potassium fluoride; 6, methanolysis of appropriate nitrile;[6] 7, bromoester + silver fluoride;[2] 8, ω-fluoroalkylmagnesium chloride + ethyl chloroformate[7]; 9, unsymmetrical anodic coupling of fluoroacid with appropriate half ester.[6] [b] Saunders and Stacey[8] report b.p. 104.5°. [c] Redemann, *et al.*[9] report b.p. 114–118°/750 mm. and n_D^{20} 1.3759. [d] Gryszkiewicz-Trochimowski[10] reports b.p. 117–118°. [e] Buckle, *et al.*[2] report b.p. 191°. [f] Buckle, *et al.*[2] report b.p. 135–138°/10 mm. [g] Buckle, *et al.*[2] report b.p. 140–141°/11 mm. [h] The details of this preparation have been described in an earlier report.[11] [i] Reaction carried out on micro-scale. [j] Oil-bath temperature using micro-distillation apparatus.[2] [k] Recrystallized from 30–60° petroleum ether.

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(6) Pattison, Stothers, and Woolford, *J. Am. Chem. Soc.*, **78**, 2255 (1956).

(7) Howell, Cott, and Pattison, forthcoming communication.

(8) Saunders and Stacey, *J. Chem. Soc.*, 1773 (1948).

(9) Redemann, Chaikin, Fearing, Rotariu, Savit, and van Hoesen, *J. Am. Chem. Soc.*, **70**, 3604 (1948).

(10) Gryszkiewicz-Trochimowski, *Rec. trav. chim.*, **66**, 430 (1947).

(11) Pattison Howell, McNamara, Schneider, and Walker, *J. Org. Chem.*, **21**, 739 (1956).

TABLE II

ω-Fluorocarboxylic Acids, Preparation, Physical Constants and Analytical Data

Compound	Formula	Method of Preparation[a]	Yield, %	B.P. °C.	B.P. Mm.	n_D^{25} or M.P., °C.	Analyses C Calc'd	Analyses C Found	Analyses H Calc'd	Analyses H Found
Fluoroacetic acid[b]	FCH_2COOH	1	93.5	167–168		31–32				
3-Fluoropropionic acid[c,d,e]	$F(CH_2)_2COOH$	2	74	83–84	14	1.3889				
		3	37	97	29	1.3888				
4-Fluorobutyric acid[c,f]	$F(CH_2)_3COOH$	2	68	76–78	5	1.3998				
		4	79	78–79	6	1.3993				
5-Fluorovaleric acid[c]	$F(CH_2)_4COOH$	2	56	90	4		50.00	49.75	7.55	7.60
		4	77	83	2	1.4080				
		5	72	80	1.75	1.4078				
6-Fluorohexanoic acid[c,g]	$F(CH_2)_5COOH$	2	47	138	26	1.4166				
		4	92	114	6	1.4159				
		5	71	130	13	1.4166				
		6	58	120–121	10					
		7	56	128–132	15	1.4165				
7-Fluoroheptanoic acid[h]	$F(CH_2)_6COOH$	5	90	133–134	10	1.4207	56.76	56.93	8.78	8.97
		8	64	132–134	10	1.4207				
		9	31.5	136–137	12					
8-Fluoroöctanoic acid[i]	$F(CH_2)_7COOH$	6	78	145–148	10	34–35	59.27	59.66	9.24	9.32
		8	65	132–133	4	35–35.5				
9-Fluorononanoic acid[j]	$F(CH_2)_8COOH$	6	87	100–101	0.15	1.4289	61.34	61.46	9.72	9.69
		8	66	89–90	0.2	1.4289				
10-Fluorodecanoic acid[c,i]	$F(CH_2)_9COOH$	2	26			48.5–49	63.16	63.09	10.00	10.04
		6	93			49–49.5				
		8	73	90–95	0.1	49–49.5				
11-Fluoroundecanoic acid[c,i]	$F(CH_2)_{10}COOH$	6	61			33–34	64.67	64.89	10.36	10.70
		8	63	113–115	0.25	36–36.5				
		9	42	98–102	0.1	35.5–36.5				
		10	94			33–34				
12-Fluorododecanoic acid[i]	$F(CH_2)_{11}COOH$	7	76			59.5–61	66.07	65.60	10.62	10.47
12-Fluorododec-2-enoic acid[i]	$F(CH_2)_9CH{:}CHCOOH$	11	31			37–37.5	66.67	66.83	9.72	9.71
13-Fluorotridec-2-enoic acid[i]	$F(CH_2)_{10}CH{:}CHCOOH$	11	34			38–39	67.82	67.93	10.00	10.05
18-Fluoroöctadecanoic acid[i]	$F(CH_2)_{17}COOH$	6	97			68.5–69	71.53	71.44	11.59	11.75
		10	90			68–69				

[a] Methods of preparation: 1, sodium salt + 100% sulfuric acid;[6] 2, fluoroalcohol oxidized by potassium dichromate and sulfuric acid;[6] 3, fluoroalcohol oxidized by nitric acid;[12] 4, methyl ester hydrolyzed by dilute sulfuric acid;[6] 5, methanolysis of appropriate nitrile followed by hydrolysis of unpurified ester (% yield based on nitrile);[6] 6, fluoroalcohol oxidized by chromium trioxide;[6] 7, nitrile hydrolyzed by conc'd hydrochloric acid;[11] 8, ω-fluoroalkylmagnesium chloride + carbon dioxide;[13] 9, ω-fluoroalkylmagnesium bromide + carbon dioxide;[13] 10, ester hydrolyzed by aq. sodium hydroxide; 11, Knoevenagel reaction between appropriate ω-fluoroaldehyde[14] and malonic acid. [b] Saunders and Stacey[8] report b.p. 167–168.5°. [c] Sodium salt prepared for toxicological and pharmacological studies. [d] Zinc salt prepared as a chemical intermediate. [e] Gryszkiewicz-Trochimowski[10] reports b.p. 78.5–79.5°/2 mm. [f] Gryszkiewicz-Trochimowski[10] reports b.p. 60–62°/2 mm. [g] Nischk and Müller[15] report b.p. 67–68°/0.6 mm. [h] M.p. *ca.* 10° and d_4^{20} 1.039. [i] Recrystallized from 30–60° petroleum ether. [j] M.p. *ca.* 18°.

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(12) Powell, Huntress, and Hershberg, *Org. Syntheses*, Coll. Vol. **1**, 168 (1941).

(13) Pattison and Howell, *J. Org. Chem.*, **21**, 879 (1956).

(14) Wilshire and Pattison, *J. Am. Chem. Soc.*, **78**, in press (1956).

(15) Nischk and Müller, *Ann.*, **576**, 232 (1952).

carbon tetrachloride;[20] (b) from oleic acid by hydroxylation with performic acid,[21] azeotropic esterification, cleavage of the glycol with lead tetraacetate,[22] reduction of the resultant ethyl azelate half-aldehyde by the method of Meerwein, Ponndorf, and Verley, conversion to 9-bromononanoic acid by conc'd sulfuric and 48% hydrobromic acids, and finally esterification with ethyl alcohol and conc'd sulfuric acid. B.p. 132°/1.8 mm.

Anal. Calc'd for $C_{11}H_{21}BrO_2$: Br, 30.19. Found; Br, 30.10.

Ethyl 16-bromohexadecanoate was prepared by esterification with conc'd sulfuric acid and ethanol of 16-bromohexadecanoic acid (4.0 g.). This acid (m.p. 69.5°; Chuit and Hausser[23] report m.p. 70–70.5°) was kindly supplied by Dr. M. Stoll, Maison Firmenich et Cie., Geneva, Switzerland. The crude bromoester was used without purification for conversion to ethyl 16-fluorohexadecanoate.

FLUOROCARBOXYLATE ESTERS

Some of the preparations listed in Table I have been or will be described elsewhere; this is indicated by appropriate references. Certain of the yields and physical constants differ slightly from those presented earlier, due to minor improvements in technique. The following preparations, subdivided according to the methods listed in Table I, are representative of those that are either new, or improvements over existing procedures.

Methods (1) and (2): treatment of sodium fluoroacetate with a dialkyl sulfate. Ethyl fluoroacetate. Technical sodium fluoroacetate (Monsanto "Compound 1080," containing 90% sodium fluoroacetate) (60 g., 0.54 mole) and diethyl sulfate (100 g., 0.65 mole) were mixed and distilled. The distillate (b.p. 115–120°) was dried over calcium sulfate and redistilled. Ethyl fluoroacetate (51 g., 90%) thus was obtained as a colorless, pleasant-smelling liquid.

Method (4): esterification of ω-fluoroacid. Methyl 7-fluoroheptanoate. A mixture of 7-fluoroheptanoic acid (25.1 g., 0.17 mole), methanol (16 g., 0.5 mole), ethylene dichloride (50.7 ml.), and conc'd sulfuric acid (0.5 ml.) was heated under reflux for 16 hours.[24] After cooling and dilution with water, the organic layer was washed with dilute sodium bicarbonate and with water. Fractionation of the dried product yielded methyl 7-fluoroheptanoate (24.4 g., 88%).

Method (5): fluorination of bromoester with potassium fluoride. Ethyl 7-fluoroheptanoate. In a 250-ml. round-bottomed flask equipped with a mercury seal stirrer and reflux condenser was placed a mixture of ethyl 7-bromoheptanoate (35 g., 0.15 mole), ethylene glycol (110 g.), and anhydrous potassium fluoride (13.55 g., 0.23 mole). The mixture was heated at 130° for eight hours with vigorous stirring. The reaction mixture was cooled, diluted with three volumes of water, and thoroughly extracted with ether. After drying over magnesium sulfate and removal of the ether, fractionation yielded ethyl 7-fluoroheptanoate (10.5 g., 40.3%).

Method (7): fluorination of bromoester with silver fluoride.[2] *Ethyl 7-fluoroheptanoate.* To ethyl 7-bromoheptanoate (11.85 g., 0.05 mole), contained in a 50-ml. round-bottomed flask equipped with a reflux condenser and calcium chloride tube, was added pure, dry silver fluoride (13.5 g., 0.11 mole). The mixture was shaken at room temperature for a few minutes, and then heated in a water-bath at 60° with constant shaking. A yellow precipitate of silver bromide was rapidly formed. The temperature was raised slowly to 80° to complete the reaction. The mixture was cooled in an ice-bath, diluted with ether (20 ml.), and filtered. The silver residue was washed thoroughly with three additional portions of ether. The combined extracts were washed with water and dried over sodium carbonate. After removal of the ether, fractionation yielded ethyl 7-fluoroheptanoate (3.0 g., 34.1%).

FLUOROCARBOXYLIC ACIDS

Some of the preparations listed in Table II have been or will be described elsewhere; this fact has been indicated by appropriate references. The following preparations, subdivided according to the methods listed in Table II, are representative of those that are either new, or improvements over existing procedures.

Method (10): hydrolysis of an ester by aqueous sodium hydroxide. 11-Fluoroundecanoic acid. This method is suitable only for those acids which have little tendency for ring closure. Ethyl 11-fluoroundecanoate (2.5 g.) and 10% aqueous sodium hydroxide (25 ml.) were heated under reflux for 40 minutes. The mixture was acidified with conc'd hydrochloric acid, cooled, and extracted with ether. The fluoroacid (2.07 g., 94%), after recrystallization from 30–60° petroleum ether, thus was obtained as a colorless solid.

Method (11): Knoevenagel reaction.[25] *13-Fluorotridec-2-enoic acid.* A mixture of 11-fluoroundecanal[14] (1.37 g., 0.0073 mole), malonic acid (0.76 g., 0.0074 mole), and piperidine (5 drops) was dissolved in pyridine (8 ml.). There was an immediate evolution of carbon dioxide. After standing for three days in the dark, the mixture was poured into water and extracted with ether. The ether extract was washed with dilute hydrochloric acid and with water, and then was extracted thoroughly with 5% aqueous sodium carbonate. After acidification of the basic solution, the fluoroacid was extracted with ether. The extracts were washed with water and dried over sodium sulfate. The ether was removed and the residual oil was left overnight in the refrigerator. The resultant crystalline mass was recrystallized from cold 30–60° petroleum ether using an acetone-Dry Ice-bath, yielding colorless needles (0.57 g., 34%).

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(22) Scanlan and Swern, *J. Am. Chem. Soc.*, **62**, 2305 (1940).

(23) Chuit and Hausser, *Helv. Chim. Acta*, **12**, 463 (1929).

(24) Clinton and Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(25) Jenny and Grob, *Helv. Chim. Acta*, **36**, 1936 (1953).