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

Toxic Fluorine Compounds. X.[1] ω-Fluorocarboxylic Acid Chlorides, Anhydrides, Amides, and Anilides

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Members of the series of ω-fluorocarboxylic acid chlorides, anhydrides, amides, and anilides were prepared and their physical constants were determined. Most of the members were used as intermediates for other work, and the solid derivatives served as a means of characterization.

The preparation and properties of the ω-fluorocarboxylic esters and acids have been described.[2] In this report is outlined the conversion of the latter to the corresponding acid chlorides and anhydrides. In most instances, the acid chlorides were converted to the amides or anilides as a means of characterization. The acid chlorides were valuable intermediates in the preparation of ω-fluorinated aldehydes, isocyanates, ketones, and β-ketoesters. The ω-fluorocarboxylic acid amides were occasionally used to prepare ω-fluoronitriles by dehydration;[3] however, this was carried out only when other methods failed.

The methods of preparation and physical constants of the ω-fluorocarboxylic acid halides are listed in Table I. 3-Fluoropropionyl chloride is rather unstable; consequently in its preparation[3] the temperature should be held below 40°.

The ω-fluorocarboxylic acid anhydrides were most conveniently prepared from the acids by treatment with isopropenyl acetate.[7] Yields, physical constants and analytical data are shown in Table II. Amides and anilides were obtained by standard procedures and are listed in Table III.

It was anticipated that the toxicity of these acid derivatives would be similar to that of the parent acids, due to hydrolysis *in vivo*. The results obtained from the very limited number tested confirm this: for example, the L.D. 50 by intraperitoneal injection into mice of 6-fluorohexanoamide was 0.70 mg./kg. and of 3-fluoropropionic anhydride was 137 mg./-kg.

EXPERIMENTAL[10]

Some of the preparations listed in Tables I, II and III have been or will be described elsewhere; this is indicated

TABLE I

ω-FLUOROCARBOXYLIC ACID HALIDES

Compound	Formula	Method of Preparation[a]	Yield, %	Boiling Point °C.	Boiling Point Mm.	n_D^{25}	Analyses Cl Calc'd	Analyses Cl Found
Fluoroacetyl chloride[b]	FCH_2COCl	1	98	70–71	740	1.3820		
		2	94	70–71	740			
Fluoroacetyl bromide[c]	FCH_2COBr	3	78	90	735			
3-Fluoropropionyl chloride	$F(CH_2)_2COCl$	4[d]	77	52	70	1.4049	32.13	32.33
4-Fluorobutyryl chloride	$F(CH_2)_3COCl$	4	75	68–70	70	1.4102	28.48	28.25
5-Fluorovaleryl chloride	$F(CH_2)_4COCl$	4	97	55–56	10	1.4194	25.58	25.33
6-Fluorohexanoyl chloride	$F(CH_2)_5COCl$	4	94	79–80	14	1.4253	23.23	23.50
7-Fluoroheptanoyl chloride	$F(CH_2)_6COCl$	4	97	92–93	13	1.4290	21.29	21.45
8-Fluorooctanoyl chloride	$F(CH_2)_7COCl$	4	87	106–107	13	1.4320	19.64	19.90
10-Fluorodecanoyl chloride	$F(CH_2)_9COCl$	4	90	132	12	1.4371	17.00	17.25
11-Fluoroundecanoyl chloride	$F(CH_2)_{10}COCl$	4	85	143–145	12	1.4397	15.95	16.01

[a] Methods of preparation: 1, sodium salt + phthalyl chloride;[4] 2, acid + phthalyl chloride; 3, acid + phosphorus tribromide; 4, acid + thionyl chloride. [b] Redemann, *et al.*[5] report b.p. 69–71°/750 mm. and n_D^{20} 1.3831. [c] Gryszkiewicz-Trochimowski, *et al.*[6] report b.p. 95–96°. [d] Reaction carried out at 35–40°.[3]

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(1) Issued as DRB Report No. SW-28.

(2) Part IX, Pattison, Hunt, and Stothers, *J. Org. Chem.* **21**, 883 (1956).

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

(4) Pattison, Fraser, Middleton, Schneider, and Stothers, *Can. J. Technol.*, **34**, 21 (1956).

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

(6) Gryszkiewicz-Trochimowski, Sporzynski, and Wnuk, *Rec. trav. chim.*, **66**, 419 (1947).

(7) Hagemeyer and Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

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

(9) Buckle, Heap, and Saunders, *J. Chem. Soc.*, 912 (1949).

(10) (a) All melting points and boiling points are uncorrected; (b) Physical constants and analytical data are listed in Tables I, II and III.

TABLE II

ω-FLUOROCARBOXYLIC ACID ANHYDRIDES

Compound	Formula	Method of Preparation[a]	Yield, %	Boiling Point °C.	Boiling Point Mm.	n_D^{25}	Analyses C Calc'd	Analyses C Found	Analyses H Calc'd	Analyses H Found
Fluoroacetic anhydride[b]	$FCH_2COOCOCH_2F$	1	82	90–93	15	1.3900				
		2	72	88–89	12	1.3903				
3-Fluoropropionic anhydride	$F(CH_2)_2COOCO(CH_2)_2F$	2	55	123–123.5	14	1.4008	43.37	43.10	4.82	5.06
6-Fluorohexanoic anhydride	$F(CH_2)_5COOCO(CH_2)_5F$	2	86	112.5–113	0.2	1.4254	57.60	57.54	8.00	7.98

[a] Methods of preparation: 1, sodium salt + acid chloride;[8] 2, acid + isopropenyl acetate.[7] [b] Saunders and Stacey[8] report b.p. 88–89°/12 mm.

TABLE III

ω-FLUOROCARBOXYLIC ACID AMIDES AND ANILIDES

Compound	Formula	Method of Preparation[a,b]	M.p., °C.	Analyses N Calc'd	Analyses N Found
Fluoroacetamide[c]	FCH_2CONH_2	1	107–108		
3-Fluoropropionamide[d]	$F(CH_2)_2CONH_2$	2	40.5–41	15.38	15.11
3-Fluoropropionanilide[e]	$F(CH_2)_2CONHC_6H_5$	3	115–116	8.38	8.33
4-Fluorobutyramide[d]	$F(CH_2)_3CONH_2$	2	106–107	13.33	13.02
5-Fluorovaleramide[f]	$F(CH_2)_4CONH_2$	2	81.5–82.5	11.76	11.48
5-Fluorovaleranilide[g]	$F(CH_2)_4CONHC_6H_5$	3	90–91	7.18	7.04
6-Fluorohexanoamide[d]	$F(CH_2)_5CONH_2$	2	78.5–79	10.53	10.69
7-Fluoroheptanoanilide[g]	$F(CH_2)_6CONHC_6H_5$	3	80.5–81	6.27	6.57
8-Fluorooctanoamide[f]	$F(CH_2)_7CONH_2$	2	92–93	8.69	8.60
10-Fluorodecanoanilide[g]	$F(CH_2)_9CONHC_6H_5$	3	72–72.5	5.28	5.37
11-Fluoroundecanoanilide[g]	$F(CH_2)_{10}CONHC_6H_5$	3	59–60	5.01	5.24

[a] Methods of preparation: 1, ester + ammonia;[9] 2, acid chloride + ammonia; 3, acid chloride + aniline. [b] With the exception of fluoroacetamide and of 3-fluoropropionamide, the preparations were carried out on a small scale simply to characterize the acid chlorides; the large-scale preparations of fluoroacetamide and of 3-fluoropropionamide[3] gave yields of 98 and 52% respectively. [c] Buckle, *et al.*[9] report m.p. 108°. [d] Recrystallized from benzene-light petroleum. [e] Recrystallized from aqueous methanol. [f] Recrystallized from light petroleum. [g] Recrystallized from ether-light petroleum.

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, are representative of those that are either new, or improvements over existing procedures.

Table I, method (3): ω-fluoroacid + phosphorus tribromide. Fluoroacetyl bromide. In a 100-ml. two-neck flask, equipped with a reflux condenser and dropping-funnel, was placed fluoroacetic acid (47.2 g., 0.606 mole). The acid was heated to boiling, and phosphorus tribromide (108 g., 0.40 mole) was added slowly over a period of one hour. After standing overnight, the mixture was distilled. The residue was treated with additional phosphorus tribromide (20 g.) and again was distilled. The total yield of fluoroacetyl bromide was 66.2 g., 78%.

Table I, method (4): ω-fluoroacid + thionyl chloride. 6-Fluorohexanoyl chloride. Thionyl chloride (40 g., 0.34 mole) was gently refluxed on a water-bath, and 6-fluorohexanoic acid (35 g., 0.26 mole) was added dropwise over a period of 90 minutes. The mixture was heated for a further 90 minutes after the addition was completed. The excess thionyl chloride was removed by distillation, and the residue was fractionated. 6-Fluorohexanoyl chloride (37.4 g., 94%) thus was obtained as a colorless, pungent-smelling liquid.

Table II, method (2): ω-fluoroacid + isopropenyl acetate. 6-Fluorohexanoic anhydride. 6-Fluorohexanoic acid (20 g., 0.15 mole), isopropenyl acetate (15 g., 0.15 mole), and conc'd sulfuric acid (2 drops) were thoroughly mixed in a flask fitted for distillation. The mixture was heated gently until all the acetone formed during the reaction had been removed. The pressure then was reduced, and the residue was fractionated, yielding 6-fluorohexanoic anhydride (16 g., 86%).

Table III, method (2): ω-fluoroacid chloride + ammonia.[11] *4-Fluorobutyramide.* A 125-ml. flask was fitted with a rubber stopper through which passed a gas delivery tube, a cold finger condenser, and a dropping-funnel with a fine tip. A groove was cut on the side of the stopper to permit escape of excess ammonia. The flask was heated on a boiling water-bath, and dry benzene (50 ml.) was introduced. Ammonia was passed through at a moderate rate, while a solution of 4-fluorobutyryl chloride (2.4 g.) in dry benzene (25 ml.) was added dropwise over a period of one hour. Ammonia was passed for a further 20 minutes after the addition was complete. The mixture was filtered through a preheated sintered-glass Buchner funnel, and the cake was washed with several portions of hot benzene. The combined filtrate and washings were concentrated by distillation, and petroleum ether (30–60°) was slowly added to the hot solution until crystallization started. The mixture was reheated until clear and then allowed to cool spontaneously. The amide was recrystallized twice from benzene-light petroleum and dried in the air.

Table III, method (3): ω-fluoroacid chloride + aniline. 3-Fluoropropionanilide. A pyridine solution of aniline was added to 3-fluoropropionyl chloride. Hydrochloric acid was added to remove the excess pyridine. The crude anilide

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[11] Philbrook, *J. Org. Chem.*, 19, 623 (1954).

was dissolved in ether and washed with water. After removal of the ether, the solid was recrystallized from aqueous methanol.

10-Fluorodecanoanilide. Aniline (3 ml.) in anhydrous benzene (25 ml.) was added dropwise to a solution of 10-fluorodecanoyl chloride (0.5 ml.) in benzene (25 ml.). After standing for 30 minutes, the mixture was washed twice with dilute hydrochloric acid and then with water. Distillation of the benzene solution dried the anilide azeotropically. The colorless crystals thus obtained were recrystallized from ether-light petroleum.

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