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

Toxic Fluorine Compounds. III.[1] ω-Fluoroalcohols

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Representative members of the series of ω-fluoroalcohols were synthesized, and their chemical, physical, and toxicological properties were determined. Most of the members were prepared by treatment of the corresponding ω-haloalcohols with potassium fluoride; an attempt was made to determine the optimum conditions for this reaction.

INTRODUCTION

A pronounced alternation in toxicity of members of the homologous series of ω-fluorocarboxylic esters, $F(CH_2)_nCOOR$, has been reported;[4,5] those esters the acid moieties of which contain an even number of carbon atoms are toxic, whereas the odd-numbered members are innocuous. Now, further members of the series have been prepared and examined for toxic properties.[2] This alternation in toxicity has been correlated with the β-oxidation theory of the breakdown of long-chain carboxylic acids in the animal body.[6] Clearly, β-oxidation of the even-numbered members would yield the toxic fluoroacetic acid in all cases, whereas the odd-numbered members would be oxidized only so far as the non-toxic 3-fluoropropionic acid.

The preparations of the ω-fluorocarboxylates required tedious individual methods for each member. It seemed desirable to find a corresponding series, all the members of which could be obtained by general methods starting from readily accessible materials. Since the biological oxidation of alcohols to acids is well established, the homologous series of ω-fluoroalcohols was examined.

Several of the lower members have already been claimed or described. Fuchs and Katscher[7] obtained an ether-soluble compound by reacting fluorosulfonic acid with polymerized formaldehyde; this material etched glass and was presumed to be fluoromethanol, although neither physical constants nor analytical data were recorded. More recently, Schrader mentioned fluoromethanol as being a suitable agent for the control of noxious animals,[8] but, after a specific enquiry, has disclaimed any knowledge of the compound.[9] Very recently, Olah and Pavlath[10] have claimed the preparation of fluoromethanol, the identity of which was supported by its conversion to benzyl fluoride on treatment with benzene and zinc chloride; however, no accurate physical constants were recorded, the analysis was in error by over 5% and no solid derivatives were prepared. Until some of these points have been clarified, the isolation and indeed the existence of pure fluoromethanol must remain uncertain. 2-Fluoroethanol has been prepared by various methods of which the following are representative: reduction of methyl fluoroacetate by lithium aluminum hydride;[11] treatment of ethylene oxide with hydrogen fluoride;[8a,12] treatment of ethylene chlorohydrin with potassium fluoride either in a solvent[13] or under anhydrous conditions in an autoclave;[14] fluorination of 2-chloro- or 2-bromo-ethyl acetate followed by hydrolysis;[15,16] thermal decomposition of tetraethanolammonium fluoride;[17] and cleavage of sodium β-hydroxyethyl sulfate by sodium fluoride.[8a] 3-Fluoropropanol has been prepared from trimethylene chlorohydrin by treatment with potassium fluoride in a solvent[18] or under anhydrous conditions in an autoclave,[19] and from 3-chloropropyl acetate by fluorination and hydrolysis.[16] 4-Fluorobutanol was obtained from 4-chlorobutyl acetate by fluorination and hydrolysis.[16]

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(1) (a) Issued as DRB Report No. SW-19. (b) Two general review articles[2,3] are considered as Parts I and II of this series. (c) To avoid ambiguity, fluorine is not referred to as a halogen throughout this communication.

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

(3) Pattison, *Nature*, **174**, 737 (1954).

(4) Saunders, *Nature*, **160**, 179 (1947).

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

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

(7) Fuchs and Katscher, *Ber.*, **62**, 2381 (1929).

(8) (a) Schrader, Brit. Intelligence Objectives Subcommittee, Rept. No. 1095; (b) German Patent Application No. J. 52,803 [I. G. Farbenindustrie Aktiengesellschaft. Leverkusen, July 11, 1935].

(9) Schrader, Private Communication to Dr. H. Martin, Science Service Laboratory, London, Canada (April 23, 1953).

(10) Olah and Pavlath, *Acta Chim. Acad. Sci. Hung.*, **3**, 203 (1953).

(11) Olah and Pavlath, *Acta Chim. Acad. Sci. Hung.*, **3**, 199 (1953).

(12) Knunyants, Kil'disheva, and Petrov, *J. Gen. Chem. U.S.S.R.*, **19**, 87 (1949) [Engl. translation].

(13) Hoffmann, *J. Am. Chem. Soc.*, **70**, 2596 (1948).

(14) Saunders, Stacey, and Wilding, *J. Chem. Soc.*, 773 (1949).

(15) Swarts, *Rec. trav. chim.*, **33**, 252 (1914).

(16) Gryszkiewicz-Trochimowski, *Rec. trav. chim.*, **66**, 427 (1947).

(17) Schrader, Brit. Intelligence Objectives Subcommittee, Rept. No. 714.

(18) Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).

(19) Buckle and Saunders, *J. Chem. Soc.*, 2774 (1949).

METHODS OF PREPARATION

Two general methods were used for preparing the majority of the ω-fluoroalcohols:

(a) $ROOC(CH_2)_{n-2}COOR \longrightarrow HO(CH_2)_nOH \longrightarrow Cl(CH_2)_nOH \longrightarrow F(CH_2)_nOH$

(b) $(CH_2)_nO + CH_3COCl \longrightarrow Cl(CH_2)_nOCOCH_3 \longrightarrow F(CH_2)_nOCOCH_3 \longrightarrow F(CH_2)_nOH$ (n = 4 or 5)

Special methods of preparation were used for obtaining 7-fluoroheptanol, 11-fluoroundecanol, and 12-fluorododecanol.

INTERMEDIATES

(*a*). *α,ω-Alkanediols* were prepared from the corresponding esters by reduction. Some yields are shown in Table I. The method and results using lithium aluminum hydride are basically the same as those described by Nystrom and Brown,[20] and by Huber.[21]

TABLE I

α,ω-ALKANEDIOLS

Alkanediol	Ester	Reducing Agent	Yield, %
1,6-Hexanediol	Diethyl adipate	$LiAlH_4$	92.5
	Diethyl adipate	$H_2 + CuCr_2O_4$	62
1,7-Heptanediol	Dimethyl pimelate	$LiAlH_4$	73
1,8-Octanediol	Dimethyl suberate	$LiAlH_4$	96
1,9-Nonanediol	Dimethyl azelate	$LiAlH_4$	65
1,10-Decanediol	Diethyl sebacate	$LiAlH_4$	99.5
	Diethyl sebacate	$H_2 + CuCr_2O_4$	82.5
1,18-Octadecanediol	Dimethyl octadecanedioate	$LiAlH_4$	78
	Dimethyl octadecanedioate	$H_2 + CuCr_2O_4$	85.7

In the reduction of dimethyl octadecanedioate to 1,18-octadecanediol using hydrogen and copper chromite, difficulties were encountered in removing traces of the catalyst from the product, and slight amounts of impurities caused complete inhibition of the reaction. These points may explain the low yield (10%) obtained by Drake, Carhart, and Mozingo[22] for this same reaction. Consequently, the use of lithium aluminum hydride proved to be more dependable for preparation of the alkanediols.

(*b*). *ω-Chloroalcohols* were most readily prepared from the corresponding alkanediols by treatment with concentrated hydrochloric acid.[23-29] For the lower members continuous extraction of the reaction mixture with 100–120° petroleum ether is essential to minimize the formation of the dichloride. By packing the extractor with Berl saddles, and hence increasing the efficiency of extraction, the yield of chloroalcohol can be raised. Some results are shown in Table II.

The partial chlorination of 1,18-octadecanediol presented difficulties: the continuous extraction method recommended by Bennett and Mosses[23] was of little value, since the glycol was extracted from the reaction flask more rapidly than it was chlorinated; the use of thionyl chloride and dimethylaniline[30] under a wide variety of conditions gave no chlorinated material; phosphorus pentachloride produced only 1,18-dichlorooctadecane. The method finally adopted involved treatment of the glycol with boiling concentrated hydrochloric acid for 24 hours, followed by extraction with petroleum ether and recovery of unchanged glycol. While the amount of chloroalcohol produced from each run was small, subsequent retreatment of the recovered glycol raised the yield to 65%.

5-Chloropentanol was more readily obtained from 5-chloroamyl acetate (see below) by transesterification, using methanol and *p*-toluenesulfonic acid.[31]

(*c*). *Miscellaneous intermediates.* 11-Bromoundecanol was prepared from undecylenyl alcohol by acetylation, addition of hydrogen bromide to the resultant undecylenyl acetate,[32] and finally transesterification. 4-Chlorobutyl acetate and 5-chloroamyl acetate were prepared in excellent yield from tetrahydrofuran and tetrahydropyran respectively by treatment with acetyl chloride.[33-36] 8-Bromooctyl acetate was prepared from sebacic acid, by the following route:

(20) Nystrom and Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).
(21) Huber, *J. Am. Chem. Soc.*, **73**, 2730 (1951).
(22) Drake, Carhart, and Mozingo, *J. Am. Chem. Soc.*, **63**, 617 (1941).
(23) Bennett and Mosses, *J. Chem. Soc.*, 1697 (1931).
(24) Bennett and Gudgeon, *J. Chem. Soc.*, 1679 (1938).
(25) Coleman and Bywater, *J. Am. Chem. Soc.*, **66**, 1821 (1944).
(26) McElvain and Carney, *J. Am. Chem. Soc.*, **68**, 2592 (1946).
(27) Price, Guthrie, Herbrandson, and Peel, *J. Org. Chem.*, **11**, 281 (1946).
(28) Campbell and Sommers, *Org. Syntheses*, Coll. Vol. **3**, 446 (1955).
(29) Perrine, *J. Org. Chem.*, **18**, 1356 (1953).
(30) Darzens, *Compt. rend.*, **152**, 1314 (1911).
(31) Fusari, Greenlee, and Brown, *J. Am. Oil Chemists' Soc.*, **28**, 416 (1951).
(32) Ashton and Smith, *J. Chem. Soc.*, 1308 (1934).
(33) Cloke and Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).
(34) Manchen and Schmidt, U. S. Patent 2,314,454 (March 23, 1943).
(35) Synerholm, *J. Am. Chem. Soc.*, **69**, 2581 (1947).
(36) Ames, Bowman, and Mason, *J. Chem. Soc.*, 174 (1950).

TABLE II

PREPARATION OF ω-CHLOROALCOHOLS

ω-Chloroalcohol	Method[a]	Solvent	Chloro-alcohol Yield, %	Dichloride Yield, %
5-Chloropentanol	II	Toluene	30	32
6-Chlorohexanol	I	Toluene	55	22.6
	III	Toluene	62.5	12.2
	IV	Toluene	64	10.0
7-Chloroheptanol	I	Petroleum Ether (100–120°)	52	15
8-Chlorooctanol	I	Petroleum Ether (100–120°)	43	10
	IV	Petroleum Ether (100–120°)	75	11
	IV	Toluene	68	6
9-Chlorononanol	I	Petroleum Ether (100–120°)	87	—
10-Chlorodecanol	I	Petroleum Ether (100–120°)	90	—
18-Chlorooctadecanol	V	Petroleum Ether (100–120°)	65	—

[a] Preparative methods used are: I, As described by Campbell and Sommers[28] and later by T. D. Perrine[29]—the glycol, hydrochloric acid, and water were heated at 95° in a continuous liquid-liquid extractor. II, As in I but heated only to 80°. III, As in I but with the extractor packed with Berl saddles up to the level of the aqueous phase. IV, As described by Coleman and Bywater[25] and by T. D. Perrine[29]: similar to I but using cuprous chloride as a promoter. V, A mixture of the glycol, conc'd hydrochloric acid, and petroleum ether (100–120°) was heated under reflux for 24 hours; recovered glycol was recycled.

$$HOOC(CH_2)_8COOH \xrightarrow[100\%]{} AgOOC(CH_2)_8COOAg$$

$$\xrightarrow[73\%]{Br_2/CCl_4} Br(CH_2)_8Br \xrightarrow[79\%\ crude]{AgOCOCH_3} Br(CH_2)_8OCOCH_3$$

FLUORINATIONS

Fluorination of the ω-chloroalcohols and of the ω-chloroalkyl acetates was most readily accomplished by use of anhydrous potassium fluoride. Conditions and yields are summarized in Table III. The reaction was carried out in two ways: either in a polyhydroxylic solvent as first recommended by Hoffmann,[13,18] or in a stainless steel autoclave under anhydrous conditions.[14,19,37]

Fluorination in polyhydroxylic solvents is the more convenient of the two methods. Observations regarding the partial fluorination of dihalides will be outlined in the next paper in this series. The following generalizations, applying to the total replacement of halide by fluoride, have emerged from this work: (a) Highest yields are obtained at a temperature lower than that suggested by Hoffmann, since this minimizes the formation of glycol ethers, one of the major side reactions. A temperature of 125 ± 5° seems to be optimum; the use of lower temperatures causes incomplete reactions. (b) Larger quantities of solvent than those suggested by Hoffmann result in increased yields. Approximately 700 g. of diethylene glycol per mole of halo-compound has been found to be satisfactory, but this ratio is not critical. (c) Purity and dryness of all reagents and solvents are essential; even slight traces of moisture lessen the yields considerably. (d) Diethylene glycol has proved to be a more effective solvent than ethylene glycol. (e) A large excess (100% or more) of potassium fluoride is always necessary. (f) Promoters, such as copper powder or potassium iodide, do not increase the yields appreciably. (g) Whenever possible, continuous removal of the fluorocompound increases the yield by minimizing the side reactions. (h) Vigorous stirring is essential. High speed stirring devices are being investigated.

If the reactants or products are unstable in polyhydroxylic solvents, the reaction may be carried out in a stainless steel autoclave using vigorous stirring and no solvent. However, only a limited number of compounds can be fluorinated satisfactorily by this method, and the large volume of the reaction bomb makes it unsuitable for small scale exploratory runs involving expensive or rare intermediates.

The fluoroalkyl acetates were hydrolyzed to the free fluoroalcohols by treatment with dilute mineral acids or with ethanolamine.[38,39]

Attempts to fluorinate 4-chlorobutyl acetate by means of potassium fluoride in anhydrous ethylene glycol at 120° led to extensive cyclization to tetrahydrofuran, but by carrying out this reaction with vigorous stirring at a low temperature, a low yield of the fluoroester was obtained. 4-Chlorobutanol could not be fluorinated directly due to preferential formation of tetrahydrofuran; since potassium fluoride in hydroxylic solvents is strongly basic, this reaction is analogous to the dehydrohalogenation of 4-chlorobutanol by alkali.[40]

5-Fluoropentanol was prepared directly from 5-chloropentanol using anhydrous potassium fluoride in anhydrous diethylene glycol. In order to mini-

(37) Gryszkiewicz-Trochimowski, Sporzynski, and Wnuk, *Rec. trav. chim.*, 66, 413 (1947).

(38) Rauscher and Clark, *J. Am. Chem. Soc.*, 70, 438 (1948).

(39) Rauscher and MacPeek, *Anal. Chem.*, 22, 923 (1950).

(40) Heine and Siegfried, *J. Am. Chem. Soc.*, 76, 489 (1954).

TABLE III

FLUORINATIONS BY MEANS OF POTASSIUM FLUORIDE

Product	Reactant	Moles of Halo-Compound	Moles of Potassium Fluoride	Solvent[a]	Temp. (°C.)	Time, hrs.	Method of Isolation[b]	Yield, %
$F(CH_2)_2OH$	$Cl(CH_2)_2OH$	4.0	6.0	E.G. + D.G.	170	—	I	44.8
$F(CH_2)_3OH$	$Cl(CH_2)_3OH$	2.69	5.76	E.G.	130 raised to 180	—	I	59.5
	$Cl(CH_2)_3OH$	1.35	3.8	A	165–170	4	III	24.5
$F(CH_2)_4OCOCH_3$	$Cl(CH_2)_4OCOCH_3$	2.74	11.2	A	230–260	48	III	66
	$Cl(CH_2)_4OCOCH_3$	0.33	0.66	E.G.	90	16	III	12.6[c]
$F(CH_2)_5OH$	$Cl(CH_2)_5OH$	.71	2.5	D.G.	160	—	II	30.2[d]
$F(CH_2)_5OCOCH_3$	$Cl(CH_2)_5OCOCH_3$	.28	0.83	D.G.	92–94	9	III	29[d]
$F(CH_2)_6OH$	$Cl(CH_2)_6OH$	.75	2.15	D.G.	125	15	IV	65
$F(CH_2)_7OH$	$Cl(CH_2)_7OH$	.6	1.5	D.G.	120–125	11	IV	62
$F(CH_2)_8OH$	$Cl(CH_2)_8OH$	.51	1.29	D.G.	120–125	13	IV	69
$F(CH_2)_8OCOCH_3$	$Br(CH_2)_8OCOCH_3$	.148	0.296	C	150	6	IV	36
$F(CH_2)_9OH$	$Cl(CH_2)_9OH$	.51	1.29	D.G.	120–125	13	IV	66
$F(CH_2)_{10}OH$	$Cl(CH_2)_{10}OH$	.52	1.29	D.G.	120–125	12	IV	64
$F(CH_2)_{11}OH$	$Br(CH_2)_{11}OH$	.14	0.28	D.G.	110	6	IV	60
$F(CH_2)_{18}OH$	$Cl(CH_2)_{18}OH$	.054	0.14	D.G.	175	6	IV	35.3

[a] Solvents: A, Autoclave (no solvent); E.G., Ethylene glycol; D.G., Diethylene glycol; C, Carbitol. [b] Isolation: I, Continuous removal under atmospheric pressure; II, Continuous removal under reduced pressure; III, Distillation after completion of the reaction; IV, Dilution with water after completion of the reaction, then extraction etc. [c] Small amounts of tetrahydrofuran were also isolated. [d] Small amounts of tetrahydropyran were also isolated.

mize the formation of tetrahydropyran, the product was continuously removed under reduced pressure as the reaction proceeded; decreasing the reaction temperature resulted in even lower yields. 5-Chloroamyl acetate was fluorinated in a similar way; while the yield was substantially the same, the great ease of preparation of 5-chloroamyl acetate makes this route more attractive for obtaining large quantities of 5-fluoropentanol.

7-Fluoroheptanol was prepared by fluorination of 7-chloroheptanol in the usual way, and by esterification and reduction (lithium aluminum hydride) of 7-fluoroheptanoic acid. This acid was obtained from 6-fluorohexylmagnesium chloride by reaction with solid carbon dioxide.[41]

11-Fluoroundecanol was prepared from 11-bromoundecanol as in Table III, and also from ethyl 11-bromoundecanoate by fluorination to ethyl 11-fluoroundecanoate (26%), followed by reduction with lithium aluminum hydride (96%).

12-Fluorododecanol was prepared from 11-fluoroundecanol by the following route:

$$F(CH_2)_{11}OH \xrightarrow[80\%]{PBr_3} F(CH_2)_{11}Br \xrightarrow[91.5\%]{NaCN} F(CH_2)_{11}CN \xrightarrow[76\%]{HCl} F(CH_2)_{11}COOH \xrightarrow[50\%]{LiAlH_4} F(CH_2)_{12}OH$$

Alternative routes to 2-fluoroethanol were investigated. None proved superior to the standard method,[18] although two showed some promise: (a) The pyrolysis of tetraethanolammonium fluoride was investigated, as suggested by Schrader.[17] Commercial tetraethanolammonium hydroxide was neutralized with 48% hydrofluoric acid, giving a poor yield of the fluoride. This on heating at 190° decomposed into 2-fluoroethanol (59%) and triethanolamine; the latter can be reconverted to tetraethanolammonium hydroxide for future use. (b) Ethylene chlorohydrin was fluorinated by treatment with ammonium fluoride in ethylene glycol (20%). In spite of the fact that ammonium fluoride is considerably more soluble than potassium fluoride in glycol, a lower yield was obtained and the distillate was slightly contaminated with ammonia.

(41) Howell and Pattison, *Chemistry & Industry*, 949 (1955).

PROPERTIES

Chemical. The ω-fluoroalcohols undergo the usual chemical reactions of the corresponding non-fluorinated alcohols, such as oxidation, acetylation, and formation of halides, ethers, and sulfonate esters. It is hoped that these reactions will be described in future reports. For identification purposes, certain of the ω-fluoroalcohols were converted into the α-naphthyl- and phenyl-urethans.

Physical. The physical constants of the ω-fluoroalcohols and of some of their precursors and derivatives are shown in Table IV.

Toxicological. The toxicity figures were obtained by intraperitoneal injection into mice, using water or propylene glycol as solvent. The results for the ω-fluoroalcohols[2] and for the corresponding ω-fluorocarboxylic acids are summarized in Table V; the latter compounds will be described in a later paper. Death was accompanied by typical fluoroacetate-like symptoms. A pronounced alternation in toxicity is apparent with ascent of the series, the

TABLE IV

PHYSICAL CONSTANTS

	B.p., °C.	Mm.	M.p., °C.	n_D^{25}	d_4^{20}
ω-CHLOROALCOHOLS					
5-Chloropentanol[a]	79–81	5		1.4512	
	91–92	11			
6-Chlorohexanol[b]	107–108	12		1.4531	
7-Chloroheptanol[c]	120–122	13		1.4550	
8-Chlorooctanol[d]	127.5–128.5	9		1.4563	
	129–130	11			
9-Chlorononanol[e]	140–142	10		1.4575	
	146–148	14			
10-Chlorodecanol[f]	90–95	0.2		1.4584	
	158–159	15			
18-Chlorooctadecanol[g]			53–54.5		
ω-FLUOROALCOHOLS					
2-Fluoroethanol[h]	100–101	742		1.3632	
3-Fluoropropanol[i]	126–127	742		1.3801	
4-Fluorobutanol[j]	57.5–58	15		1.3942	
5-Fluoropentanol	163–166	745		1.4057	
	70–71	11			
6-Fluorohexanol	85–86	14		1.4141	0.975
	79–81	9			
7-Fluoroheptanol	98–99	12		1.4197	.956
8-Fluorooctanol	111.5–112	12		1.4248	.945
	106–107	10			
9-Fluorononanol	125–126	15		1.4279	.928
10-Fluorodecanol	131.5–132	10	*ca.* 22[m]	1.4322	.919
	136–137	15			
11-Fluoroundecanol	118–120	3	*ca.* 19[m]	1.4364	
12-Fluorododecanol	88–92	0.15	*ca.* 25[m]	1.4391	
18-Fluorooctadecanol	140–141	0.01	60.7–61		
ω-FLUOROALKYL ACETATES					
4-Fluorobutyl acetate[k]	56–57	12		1.3949	
5-Fluoroamyl acetate	71–72.5	11			
8-Fluorooctyl acetate	96–97	6		1.4225	
ω-FLUOROALKYL α-NAPHTHYLURETHANS					
6-Fluorohexyl α-naphthylurethan			59		
7-Fluoroheptyl α-naphthylurethan			49		
8-Fluorooctyl α-naphthylurethan			53.5		
9-Fluorononyl α-naphthylurethan			63		
10-Fluorodecyl α-naphthylurethan			70		
ω-FLUOROALKYL PHENYLURETHANS					
8-Fluorooctyl phenylurethan			55.5–56		
10-Fluorodecyl phenylurethan			62–63		
11-Fluoroundecyl phenylurethan			54.5–55		
MISCELLANEOUS					
7-Fluoroheptanoic acid	132–134	10		1.4207	1.039
Methyl 7-fluoroheptanoate	92.5–93.5	13		1.4101	
11-Bromoundecanol	134–136	0.3	43–44		
Ethyl 11-fluoroundecanoate[l]	145–146	9		1.4257	
11-Fluoroundecyl bromide	95–96	0.6		1.4518	
12-Fluorododecanonitrile	114–115	0.9		1.4320	
12-Fluorododecanoic acid			59.5–61		
Tetraethanolammonium fluoride			189–190		

[a] McElvain and Carney[26] report b.p. 112° (12 mm.) and n_D^{20} 1.4518. [b] Coleman and Bywater[25] report b.p. 114–117° (20 mm.) and n_D^{20} 1.4550. [c] Perrine[29] reports b.p. 122–124° (12 mm.) and n_D^{25} 1.4559. [d] Perrine[29] reports b.p. 130–140° (10 mm.) and n_D^{25} 1.4572; Altman[42] reports b.p. 139° (18.5 mm.). [e] Altman[42] reports b.p. 146.5° (14 mm.). [f] Price, *et al.*[27] report b.p. 126–128° (2 mm.) and n_D^{20} 1.4578. [g] Bennett and Gudgeon[24] report m.p. 53–54.5°. [h] Saunders, *et al.*[14] report b.p. 103.5°; Gryszkiewicz-Trochimowski[16] reports b.p. 101°; Hoffmann[18] reports b.p. 103.3° and n_D^{25} 1.3633. [i] Hoffmann[18] reports b.p. 127.8° and n_D^{25} 1.3771. [j] Gryszkiewicz-Trochimowski[16] reports b.p. 52–53° (11 mm.). [k] Gryszkiewicz-Trochimowski, *et al.*[37] report b.p. 55.5–56° (11 mm.). [l] Buckle, *et al.*[5] report b.p. 140–141° (11 mm.). [m] M.p. not determined accurately.

(42) Altman, *Rec. trav. chim.*, **57**, 941 (1938).

compounds containing an even number of carbon atoms being toxic, and those with an odd number non-toxic. With a few exceptions, the toxicity data show a striking parallelism between the corresponding members of the two series; this is in contrast to the figures presented earlier[2,5] for the ω-fluorocarboxylic *esters*, which were consistently less toxic than the corresponding ω-fluoroalcohols.

TABLE V

TOXICITIES

Formula of ω-Fluoroalcohol	L.D. 50 for mice (mg./kg.)	Formula of Corresponding ω-Fluorocarboxylate	L.D. 50 for mice (mg./kg.)
FCH_2CH_2OH	10	FCH_2COOH	6.6
$F(CH_2)_3OH$	46.5	$F(CH_2)_2COOH$	60
$F(CH_2)_4OH$[a]	0.9	$F(CH_2)_3COONa$	0.65
$F(CH_2)_5OH$	>100	$F(CH_2)_4COOH$	>100
$F(CH_2)_6OH$[a]	1.24	$F(CH_2)_5COOH$	1.35
$F(CH_2)_7OH$	80.0	$F(CH_2)_6COOH$	40
$F(CH_2)_8OH$	0.6	$F(CH_2)_7COOH$	0.64
$F(CH_2)_8OAc$	1.3		
$F(CH_2)_9OH$	32.0	$F(CH_2)_8COOH$	>100
$F(CH_2)_{10}OH$	1.0	$F(CH_2)_9COOH$	1.5
$F(CH_2)_{11}OH$	>100	$F(CH_2)_{10}COOH$	57.5
$F(CH_2)_{12}OH$	1.5	$F(CH_2)_{11}COOH$	1.25
$F(CH_2)_{18}OH$	4.0	$F(CH_2)_{17}COOH$	5.7

[a] For comparison, both $Cl(CH_2)_4OH$ and $Cl(CH_2)_6OH$ had L.D. 50 >100 mg./kg.

EXPERIMENTAL[43]

α,ω-Dicarboxylic esters. Diethyl adipate and diethyl sebacate were readily prepared by the method of van Rysselberge.[46] The dimethyl esters of pimelic, suberic, and azelaic acids were most conveniently synthesized by boiling overnight a mixture of the acid (1 mole), absolute methanol (6 moles), ethylene chloride (600 ml.), and concentrated sulfuric acid (6 ml.).[47] By this procedure, dimethyl pimelate was obtained in 90% yield, b.p. 120–121° (10 mm.), n_D^{22} 1.4302; dimethyl suberate in 92% yield, b.p. 133° (10 mm.), n_D^{25} 1.4319; and dimethyl azelate in 87% yield, b.p. 145–148° (12 mm.), n_D^{22} 1.4332.

Methyl hydrogen sebacate was prepared by the method of Swann, Oehler, and Buswell,[48] but modified as follows: sebacic acid, dimethyl sebacate, methanol, and *n*-butyl ether were heated under reflux until the mixture became homogeneous (*ca.* 2 hours). Concentrated hydrochloric acid then was added and the mixture was heated under reflux for three hours and then for a further three hours after the addition of more methanol. The isolation of the half ester was carried out as in the original method. By using this modified procedure, the time for completing the reaction was reduced by five hours, and the yield was consistently 65% or better. B.p. 205–207° (15 mm.).

Dimethyl octadecanedioate was synthesized by anodic coupling of methyl hydrogen sebacate;[49] recrystallization from methanol gave as satisfactory a product as that obtained by distillation, the recommended procedure.

α,ω-Alkanediols. Reduction of the dibasic esters was accomplished by the use of either hydrogen and copper chromite[50] or lithium aluminum hydride.[20,21] The latter method proved preferable since consistently good yields on a large scale were readily obtained. The catalytic hydrogenation method was less satisfactory because of the wide variations in yield with each catalyst preparation, the small capacity of the hydrogenation bomb and the difficult isolations of certain members. The esters reduced and results obtained are summarized in Table I. The following examples are representative:

(*a*). *1,8-Octanediol.* Dimethyl suberate (130 g., 0.64 mole) was added dropwise to a stirred solution of lithium aluminum hydride (30 g., 0.79 mole) in anhydrous ether (1000 ml.). When the addition was complete, the mixture was cooled in an ice-bath and excess lithium aluminum hydride was decomposed by water. The reaction mixture was poured onto ice and the complex was hydrolyzed with 900 ml. of 10% sulfuric acid. The aqueous layer then was extracted with several portions of ether. After drying over potassium carbonate, concentration of the extracts gave 87.0 g. (93%) of 1,8-octanediol, m.p. 56.5–57.5°.

With the lower glycols continuous extraction of the hydrolyzate is essential for maximum yield.

(*b*). *1,18-Octadecanediol.* (Method I). Dimethyl octadecanedioate (19.4 g., 0.057 mole) and a copper chromite catalyst (1.5 g.) were placed in a Parr high-pressure hydrogenator. The bomb was closed, filled with hydrogen at 1800 p.s.i., sealed, and then heated to 255° for six hours with continuous shaking. The cold product was dissolved in alcohol and filtered from the catalyst. Two recrystallizations from benzene gave 14.0 g. (85.7%) of a colorless solid, m.p. 98°.

(*c*). *1,18-Octadecanediol.* (Method II). To lithium aluminum hydride (4.5 g., 0.118 mole) in 250 ml. of anhydrous ether was slowly added with stirring dimethyl octadecanedioate (33.9 g., 0.099 mole) in 300 ml. of anhydrous benzene. The stirring was continued for two hours after the addition was complete. Water and then sulfuric acid (10%) were added in the usual way. The mixture was extracted several times with hot benzene. The extract was washed several times with hot water and then the benzene was stripped off, thereby removing any residual water as the azeotrope. The residue was recrystallized from benzene, yielding 22.2 g. (78%) of a colorless solid, m.p. 97°.

ω-Chloroalcohols. These were synthesized essentially by the method of Campbell and Sommers.[28] The modifications in technique employed and the results obtained are summarized in Table II. Some typical preparations are given below:

(*a*). *5-Chloropentanol.* A mixture of 1,5-pentanediol (92.5 g., 0.89 mole), concentrated hydrochloric acid (685 ml.), and water (150 ml.) was heated on a water-bath

(43) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and some by the Clark Microanalytical Laboratory, Urbana, Illinois, and by Dr. Rob. Dietrich, Zurich, Switzerland. The fluorine determinations were carried out in the authors' laboratory, either by the lead chlorofluoride method[44] or by the amperometric method[45] using aluminum chloride and Superchrome Garnet Y. Results are shown in Table VI. (b) The melting points were determined with the Fisher-Johns melting point apparatus. (c) The melting points and boiling points are uncorrected. (d) Intermediates which were obtained from commercial sources were purified just before use.

(44) Chapman, Heap, and Saunders, *Analyst*, **73**, 434 (1948).

(45) Castor and Saylor, *Anal. Chem.*, **24**, 1369 (1952).

(46) van Rysselberge, *Bull. soc. chim. Belg.*, **35**, 311 (1926); Micovic, *Org. Syntheses*, Coll. Vol. 2, 264 (1943).

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

(48) Swann, Oehler, and Buswell, *Org. Syntheses*, Coll. Vol. 2, 276 (1943). The modified procedure was originally carried out by S. B. D. Hunt in this laboratory.

(49) Greaves, Linstead, Shephard, Thomas, and Weedon, *J. Chem. Soc.*, 3326 (1950); see also Swann, Oehler, and Pinkney, *Org. Syntheses*, **21**, 48 (1941).

(50) Lazier, Hill, and Amend, *Org. Syntheses*, Coll. Vol. 2, 325 (1943).

TABLE VI

ANALYTICAL DATA

Compound	C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found	Halogen Calc'd	Halogen Found
$Br(CH_2)_{11}OH$							Br, 31.87	32.09
$F(CH_2)_4OH$							F, 20.65	20.8
$F(CH_2)_5OH$							F, 17.92	17.6
$F(CH_2)_5OCOCH_3$	56.75	56.95	8.83	9.02				
$F(CH_2)_6OH$							F, 15.83	15.6
$F(CH_2)_6COOH$	56.75	56.93	8.83	8.97				
$F(CH_2)_6COOCH_3$	59.27	59.16	9.26	9.26				
$F(CH_2)_7OH$	62.69	62.39	11.19	11.20				
$F(CH_2)_8OH$	64.86	64.58	11.48	11.34				
$F(CH_2)_9OH$	66.67	66.61	11.73	11.53				
$F(CH_2)_{10}OH$							F, 10.80	10.9
$F(CH_2)_{10}COOEt$	67.20	67.19	10.85	10.74			F, 8.19	8.0
$F(CH_2)_{11}OH$	69.40	69.34	12.18	11.87				
$F(CH_2)_{11}Br$							Br, 31.62	31.40
$F(CH_2)_{11}CN$					7.01	6.71		
$F(CH_2)_{11}COOH$	66.07	65.60	10.62	10.47				
$F(CH_2)_{12}OH$	70.60	70.45	12.26	12.34				
$F(CH_2)_{18}OH$	75.01	75.16	12.84	13.01			F, 6.59	6.4
$F(CH_2)_6OCONHC_{10}H_7$					4.84	4.72		
$F(CH_2)_7OCONHC_{10}H_7$					4.62	4.59		
$F(CH_2)_8OCONHC_{10}H_7$					4.42	4.45		
$F(CH_2)_8OCONHC_6H_5$					5.24	5.51		
$F(CH_2)_9OCONHC_{10}H_7$					4.23	4.25		
$F(CH_2)_{10}OCONHC_{10}H_7$					4.05	4.22		
$F(CH_2)_{10}OCONHC_6H_5$					4.74	4.65		
$F(CH_2)_{11}OCONHC_6H_5$	69.86	70.03	9.12	8.80				
$(HOCH_2CH_2)_4N^+F^-$							F, 8.91	9.0

at 80° while being continuously extracted with toluene for 15 hours using a continuous liquid-liquid extractor.[28] After cooling, the toluene extracts were separated, dried over potassium carbonate, and concentrated under reduced pressure. Fractionation of the residue gave first a forerun of 40 g. (32%) of 1,5-dichloropentane, b.p. 68° (11 mm.), n_D^{25} 1.4551, and then 32 g. (30%) of 5-chloropentanol.

5-Chloropentanol was also obtained from 5-chloroamyl acetate by transesterification using methanol and *p*-toluenesulfonic acid.[31] After removal of the methyl acetate, the product was filtered, washed with saturated sodium bicarbonate, dried over sodium sulfate, and distilled.

(*b*). *10-Chlorodecanol.* 1,10-Decanediol (100 g., 0.58 mole), concentrated hydrochloric acid (470 ml.), and water (130 ml.) were heated on a water-bath at 95–100° and continuously extracted as above with petroleum ether (100–120°) for 12–14 hours. The product was isolated as described for 5-chloropentanol. Combination of the products from four such runs and fractionation gave 335 g. (78%) of 10-chlorodecanol. This yield was later raised to 90% by employing 800 ml. of 9 *N* hydrochloric acid and extracting for 24 hours as recommended by Perrine.[29]

(*c*). *18-Chlorooctadecanol.* A mixture of 1,18-octadecanediol (21.5 g., 0.075 mole), 100–120° petroleum ether (15 ml.), and concentrated hydrochloric acid (200 ml.) was heated under reflux for 24 hours. A further quantity of petroleum ether (100 ml.) then was added, and the hot extract was decanted. The extract was cooled, and the precipitated glycol was filtered off and returned to the reaction flask together with a further quantity of hydrochloric acid (20 ml.) and petroleum ether (15 ml.). The mixture was again heated under reflux for 24 hours. After five days of this treatment, only 6.5 g. of diol remained unchanged. The extracts were combined, the petroleum ether was distilled off, and the residue was taken up in 250 ml. of petroleum ether (30–60°). After standing for several hours at room temperature, the last traces of diol precipitated and were filtered off. The petroleum ether was removed and the residue was taken up in methanol. On cooling, any dichloride present precipitated and was filtered off. After removal of the methanol, the solid residue was recrystallized three times from petroleum ether (30–60°). A yield of 10.4 g. (65% based on reacted diol) was obtained.

11-Bromoundecanol. Anhydrous hydrogen bromide was bubbled through undecylenyl acetate in the presence of benzoyl peroxide forming 11-bromoundecyl acetate[32]; the crude bromoester then was converted to 11-bromoundecanol by transesterification[31] using methanol and *p*-toluenesulfonic acid, with continuous removal of the resultant methyl acetate. The bromoalcohol, obtained in 74% yield (based on undecylenyl acetate), was recrystallized from 30–60° petroleum ether or from aqueous methanol.

4-Chlorobutyl acetate[33,34] and *5-chloroamyl acetate*[35,36] were synthesized from tetrahydrofuran and tetrahydropyran by treatment with a slight excess of acetyl chloride. By using 2.2 g. of zinc chloride per mole of cyclic ether, the esters were obtained in yields of 80% and 95% respectively.

1,8-Dibromooctane. An aqueous solution of anhydrous sodium carbonate (54 g., 0.51 mole) was added slowly and with stirring to sebacic acid (101 g., 0.50 mole) in aqueous ethanol. When the solution became clear and no more carbon dioxide was evolved, an aqueous solution of silver nitrate (170 g., 1.0 mole) was added with stirring. The precipitate of silver sebacate was washed thoroughly with water and then with acetone. Finally it was dried at 80–100° for 12 hours. Yield: 208 g. (100%). Silver sebacate (120 g., 0.288 mole) was added slowly to a stirred and warmed solution of bromine (110 g., 0.69 mole) in carbon tetrachloride (600 ml.) contained in an open beaker. After removal of the silver bromide by filtration, the solvent and excess bromine were removed *in vacuo*. The residue was washed with aqueous sodium hydroxide (10%) and then with water, and the neutral fraction was extracted with ether. The ether solution was dried over calcium chloride. After removal of

the ether, the product was distilled, yielding 57.3 g. (73%) of a colorless liquid, b.p. 148–153° (13–15 mm.). Oldham[51] reports b.p. 140° (5 mm.).

8-Bromooctyl acetate. 1,8-Dibromooctane (50.8 g., 0.187 mole), silver acetate (34.4 g., 0.206 mole), and glacial acetic acid (300 ml.) were cautiously heated under reflux with stirring. Silver bromide precipitated in large particles, leaving a clear supernatant liquid. Most of the acetic acid was removed by distillation and the residue was extracted with ether. The extracts were washed with water, dried, and distilled. A colorless liquid (37.1 g., 79% crude) was obtained, of b.p. 149–159° (15–16 mm.). This consisted of 8-bromooctyl acetate, contaminated with 1,8-dibromooctane and octamethylene diacetate. Because of the close boiling points of these three compounds, no attempt was made to fractionate the mixture, and the crude material was used directly in the subsequent fluorination.

ω-Fluoroalcohols. Results of the fluorinations are summarized in Table III. Some observations regarding optimum conditions are given above.

Commercial samples of ethylene glycol and diethylene glycol were purified by distillation to constant boiling point and refractive index. Potassium fluoride (Baker and Adamson, anhydrous, purified) was dried at 160° for 24 hours, ground finely in a mortar or a ball mill, and then dried again; before use, it was ground once again while still hot and then stored in the oven at 160° for an additional 48 hours.

The preparation of *6-fluorohexanol* is given as a typical example. A mixture of 6-chlorohexanol (103 g., 0.75 mole), anhydrous potassium fluoride (125 g., 2.15 moles), and diethylene glycol (500 g.) was placed in a 1-liter three-necked flask fitted with a thermometer, reflux condenser, and precision-bore stirrer (Hershberg type). The reaction mixture was stirred vigorously while being heated at 125° for 15 hours. After cooling, the reaction mixture was poured into an equal volume of water and extracted several times with ether. After drying over calcium sulfate ("Drierite"), the extracts were concentrated and the residue was fractionated under reduced pressure. Following a small fraction of low-boiling unsaturated material, 59 g. (65%) of 6-fluorohexanol were collected.

Using this method of isolation (IV, see Table III), it was found that in the case of the higher alcohols, particularly 9-fluorononanol and 10-fluorodecanol, the small amount of diethylene glycol extracted from the aqueous medium distilled as an azeotropic mixture with the fluoroalcohol. This difficulty was overcome by washing the concentrated extracts with water prior to distillation.

18-Fluorooctadecanol, prepared by the method summarized in Table III, was extracted from the diluted mixture with benzene, and recrystallized three times from petroleum ether (30–60°).

Hydrolysis of fluoroalkyl acetates. The following reactions are representative:

(*a*). *4-Fluorobutyl acetate.* The ester was heated under reflux with 5% sulfuric acid (3.5 volumes) for 30 minutes. After cooling, an excess of solid sodium bicarbonate was added. The mixture was extracted several times with ether, and the extract was dried over sodium sulfate and then over potassium fluoride. The ether was removed and the residue was distilled, giving 4-fluorobutanol (85.6%).

(*b*). *5-Fluoroamyl acetate.* The ester was heated under reflux with 10% hydrochloric acid (3–4 volumes) for 30 minutes. Isolation as in (*a*) above gave 5-fluoropentanol (87%).

(*c*). *8-Fluorooctyl acetate.* The ester (10 g., 0.053 mole) was heated under reflux with pure ethanolamine (30 ml.) for 30 minutes. The solution was cooled, extracted with ether three times, washed with a very small quantity of water, dried, and distilled. 8-Fluorooctanol (4.3 g., 55%) was obtained as a colorless liquid.

Phenyl- and α-naphthyl-urethan derivatives of the ω-fluoroalcohols were prepared in the manner recommended by Shriner, Fuson, and Curtin[52]: the ω-fluoroalcohol (1 g.) was placed in a small test tube and the isocyanate (10% excess) was added. The resultant mixture was warmed on the steam-bath for 15 minutes. On cooling, a white crystalline precipitate was obtained, which was recrystallized several times from petroleum ether (100–120°).

7-Fluoroheptanol was prepared from 7-fluoroheptanoic acid[41] by conversion[47] to methyl 7-fluoroheptanoate (88%), followed by reduction with lithium aluminum hydride (87%) as described below for the preparation of 11-fluoroundecanol.

Ethyl 11-fluoroundecanoate. In a 500-ml. round bottom flask equipped with a mercury seal stirrer and reflux condenser were placed ethyl 11-bromoundecanoate (98 g., 0.334 mole, n_D^{20} 1.4612, obtained from undecylenic acid by addition of hydrogen bromide[53] and then esterification),[5] ethylene glycol (100 ml.), and anhydrous potassium fluoride (29 g., 0.5 mole). The mixture was heated at 130–140° for 12 hours, with vigorous stirring. Water (400 ml.) was added and the fluoroester was separated. The aqueous glycol was extracted twice with ether and the extracts were added to the crude ester. To this ethereal solution was added a solution of bromine in ether until a distinct yellow color persisted. The extracts were dried over sodium sulfate. After removal of the ether, the high-boiling residue on fractionation *in vacuo* yielded 21.1 g. (26%) of ethyl 11-fluoroundecanoate.

11-Fluoroundecanol. To lithium aluminum hydride (7 g., 0.18 mole) in 200 ml. of anhydrous ether was slowly added with stirring ethyl 11-fluoroundecanoate (57.8 g., 0.237 mole) in 200 ml. of anhydrous ether. After stirring for an additional 15 minutes, water was added dropwise to the mixture with care until all effervescence had ceased. Sulfuric acid (20%) then was added until the mixture became clear. The ethereal layer was separated and the aqueous layer was extracted several times with fresh ether. The ethereal extracts were combined, and a solution of bromine in ether was added until a distinct yellow color persisted. The extracts were dried over sodium sulfate. After removal of the ether, the residue was fractionated, and 45.5 g. (96%) of 11-fluoroundecanol were obtained.

11-Fluoroundecyl bromide. To 11-fluoroundecanol (36.3 g., 0.195 mole) was added redistilled phosphorus tribromide (19 g., 0.07 mole) slowly and with stirring and cooling. After the addition was complete, the mixture was warmed to room temperature and finally was heated at 85° for 30 minutes. The mixture then was cooled, diluted with water, and extracted with ether. The ether extract was washed with dilute sodium carbonate solution and then with water. The ether was removed from the solution after it had been dried over calcium chloride. The residue was fractionated *in vacuo* yielding 39.8 g. (80%) of 11-fluoroundecyl bromide.

12-Fluorododecanonitrile. Sodium cyanide (7.63 g., 0.155 mole) and 11-fluoroundecyl bromide (26.2 g., 0.107 mole) in 80% ethanol (22.2 ml.) were heated under reflux for seven hours, and then an excess of water was added. The solution was extracted with ether and the extract was dried over sodium sulfate. The ether was removed and the residue was fractionated. A yield of 19.5 g. (91.5%) of 12-fluorododecanonitrile was obtained.

12-Fluorododecanoic acid. 12-Fluorododecanonitrile (15 g., 0.075 mole) and concentrated hydrochloric acid (200 ml.) were heated under reflux for 22 hours. Previously the hydrolysis had been attempted using shorter periods of time

(51) Oldham, *J. Chem. Soc.*, 100 (1950). The method described above is a simplification of that of Oldham.

(52) Shriner, Fuson, and Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 211.

(53) Ashton and Smith, *J. Chem. Soc.*, 435 (1934).

(3, 5, and 15 hours), but in each instance the reaction had been found to be incomplete. On cooling, the acid crystallized, and was purified by recrystallization from petroleum ether (30–60°). A yield of 12.5 g. (76%) was obtained.

12-Fluorododecanol. To a solution of lithium aluminum hydride (2.1 g., 0.055 mole) in 100 ml. of anhydrous ether was added dropwise and with vigorous stirring a solution of 12-fluorododecanoic acid (11 g., 0.05 mole) in 100 ml. of anhydrous ether. The mixture was heated under reflux for 15 minutes after the addition was complete. Water was added dropwise, and, when effervescence had ceased, 10% sulfuric acid (300 ml.) was introduced cautiously. The ethereal layer was separated, washed, and dried over sodium sulfate. Fine, needle-like crystals, which proved to be inorganic, separated from the ether solution. These were filtered off and the ether was removed. The residue on fractionation yielded 5 g. (50%) of 12-fluorododecanol.

Alternative routes to 2-fluoroethanol. (*a*). Tetraethanolammonium hydroxide (48% technical grade) was evaporated *in vacuo* to half volume. Acetone was added, forming a viscous oil. The aqueous acetone layer was decanted off, and just sufficient methanol was added to the oil to dissolve it. Aqueous hydrofluoric acid (48%) was added until the mixture was neutral to litmus. A small amount of acetone was added to precipitate the fluoride. After several recrystallizations from methanol using Norit, colorless crystals were obtained, m.p. 189–190°. When these were heated at 190° for several hours, 2-fluoroethanol was obtained (59% based on tetraethanolammonium fluoride).

(*b*). The standard procedure[13] was modified by using ammonium fluoride in place of the usual potassium fluoride. Yield: 20%.

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