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

Toxic Fluorine Compounds. IV.[1] ω-Fluoroalkyl Halides

F. L. M. PATTISON AND W. C. HOWELL

Received January 31, 1956

Representative members of the series of ω-fluoroalkyl halides were synthesized, and their chemical, physical, and toxicological properties were determined. Evidence was obtained for the hydrolysis *in vivo* of aliphatic halogen compounds.

INTRODUCTION

In an earlier report[2] were described the preparation and properties of members of the series of ω-fluoroalcohols, $F(CH_2)_nOH$. Their toxicology was shown to conform to the pattern established for the ω-fluorocarboxylates,[3] $F(CH_2)_nCOOR$, that is, an alternation in toxicity on ascent of the series. This striking difference between the odd and even members of the two series suggested that the same pattern might be apparent in other series of ω-fluorocompounds, and hence that the toxicology of the members might well be of value as a means of demonstrating *in vivo* conversions of functional groups. The broad aspects of this idea have already been reviewed;[4,5] in general, toxicological results have provided *a priori* evidence for the mode of biochemical breakdown of various aliphatic functional groupings, including nitriles, amines, nitroalkanes, thiocyanates, mercaptans, etc. Amongst the most important intermediates for synthesizing new types of ω-fluorocompounds were the ω-fluoroalkyl halides, and it was primarily for this reason that their preparation and properties were examined. Moreover, it was hoped that their toxicological properties would provide information regarding the biochemical breakdown of aliphatic halogen compounds.

A survey of the literature reveals that the following methods have been used for the preparation of at least one member of the ω-fluoroalkyl halide series:

(1) $X(CH_2)_nX + MF \longrightarrow F(CH_2)_nX + MX$ ($M = K, Hg^+, {}^1/_2Hg^{++}$)

(2) $3\ F(CH_2)_nOH + PBr_3 \longrightarrow 3\ F(CH_2)_nBr + H_3PO_3$

(3) $F(CH_2)_nOH + SOCl_2 \longrightarrow F(CH_2)_nCl + SO_2 + HCl$

(4) $F(CH_2)_nOSO_2R + KX \longrightarrow F(CH_2)_nX + KOSO_2R$

(5) $X(CH_2)_nOSO_2R + KF \longrightarrow X(CH_2)_nF + KOSO_2R$

(6) $F_2 + X_2 \longrightarrow 2\ FX$; $FX + CH_2{=}CH_2 \longrightarrow F(CH_2)_2X$

(7) $X(CH_2)_nOSO_2OK + KF \longrightarrow X(CH_2)_nF + K_2SO_4$

The members previously prepared by these methods are listed in Table I.

TABLE I

PREVIOUS PREPARATIONS OF ω-FLUOROALKYL HALIDES

Compound	Method of Preparation[a]	Yield, %	References
2-Fluoroethyl chloride	3	44–69.4	6, 7, 8
	5	60–77	9, 10
	6	[b]	11
2-Fluoroethyl bromide	1	24–50	7, 12, 13, 14
	2	48–51	6, 7
	5	35–61.5	9, 10, 15
	6	[b]	11
	7	27	16
2-Fluoroethyl iodide	1	[c]	13
	4	[d]	17
3-Fluoropropyl chloride	3	81.3	7
	5	65	10
3-Fluoropropyl bromide	1	22–31	7, 12, 18
	2	70.6	7
4-Fluorobutyl chloride	1	36.6	7, 12
	5	64	10
4-Fluorobutyl bromide	1	19.6	7
5-Fluoroamyl chloride	1	17–38.5	7, 12, 18
	5	66	10
5-Fluoroamyl bromide	1	31.4	7

[a] Methods of preparation correspond to the numbered equations. [b] No experimental details given. [c] Yield stated to be quite small. [d] No experimental details given, but later prepared in this laboratory in 66% yield.

(1) (a) Issued as DRB Report No. SW-20. (b) To avoid ambiguity, fluorine is not generally referred to as halogen in this communication.

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

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

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

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

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

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

(8) Thomas, U. S. Patent 2,673,884 (March 30, 1954).

(9) Razumovskii and Fridenberg, *Zhur. Obshchei Khim.*, **19**, 92 (1949).

(10) Pattison and Millington, *Can. J. Chem.*, **34**, 757 (1956).

(11) Schrader, Brit. Intelligence Objectives Subcommittee, Rept. No. 1808.

(12) Hoffmann, *J. Org. Chem.*, **14**, 105 (1949).

(13) Henne and Renoll, *J. Am. Chem. Soc.*, **58**, 889 (1936).

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

(15) Edgell and Parts, *J. Am. Chem. Soc.*, **77**, 4899 (1955).

(16) Schrader, Private Communication to Dr. H. Martin, Science Service Laboratory, London, Canada (February 26, 1954).

(17) Knunyants, Kil'disheva and Bykhovskaya, *J. Gen. Chem. (U.S.S.R.)*, **19**, 93 (1949) [Engl. translation.]

(18) Bruce and Huber, *J. Am. Chem. Soc.*, **75**, 4668 (1953).

TABLE II

PARTIAL FLUORINATIONS OF ω,ω'-DIHALOGENOALKANES BY MEANS OF POTASSIUM FLUORIDE

Product	Reactant	Moles of Dihalide	Moles of Potassium Fluoride	Solvent[a]	Temp., °C.	Pressure, mm.	Time, hrs.	Method of Isolation[b]	Yield, %
$F(CH_2)_3Cl$	$Cl(CH_2)_3Cl$	1.0	1.55	D.G.	125–130	740	3	II	25
$F(CH_2)_3Br$	$Br(CH_2)_3Br$	2.48	2.86	D.G.	90–100	200	4	III	24.5
$F(CH_2)_4Cl$	$Cl(CH_2)_4Cl$	4.0	6.0	E.G.	120	740	20	I	29
		2.0	3.0	D.G.	120	400	5	III	50.5
$F(CH_2)_4Br$	$Br(CH_2)_4Br$	1.57	2.43	E.G.	105	740	8	I	16.5
		1.59	2.39	D.G.	95–105	100–200	4	III	27.5
$F(CH_2)_5Cl$	$Cl(CH_2)_5Cl$	0.92	1.50	E.G.	130	740	8	I	27
		1.42	2.16	D.G.	125	100–200	4	III	51
$F(CH_2)_5Br$	$Br(CH_2)_5Br$	1.74	2.60	E.G.	105–110	740	6	I	28
		0.65	1.45	D.G.	100	13	4	III	48.5
$F(CH_2)_6Cl$	$Cl(CH_2)_6Cl$	1.17	1.75	E.G.	130	740	8	I	17
		1.08	1.65	D.G.	125	90–100	4	III	56.5
$F(CH_2)_6Br$[c]	$Br(CH_2)_6Br$	1.08	1.65	D.G.	110	15–30	4	III	38
$F(CH_2)_7Cl$	$Cl(CH_2)_7Cl$	0.92	1.40	D.G.	125	40–50	4	III	48.5
$F(CH_2)_8Br$	$Br(CH_2)_8Br$	0.05	0.2	C	110	740	8	I	10

[a] Solvents: E.G., Ethylene glycol; D.G., Diethylene glycol; C, Carbitol. [b] Isolation: I, Dilution with water, then separation and distillation; II, Dropwise addition of reactant and continuous removal of the product; III, Reactants mixed prior to reactions, then continuous removal of the product. [c] Some indication of the by-products formed in these fluorinations is given by the isolation in this case of $Br(CH_2)_6O(CH_2)_2O(CH_2)_2O(CH_2)_6Br$ (b.p. 115° (0.1 mm.) and n_D^{25} 1.4729), resulting from loss of hydrogen bromide between hexamethylere dibromide and the solvent.

METHODS OF PREPARATION

For preparing ω-fluoroalkyl chlorides and bromides, methods (1), (2), (3) and (5) proved to be most convenient; the latter has been described elsewhere.[10] Iodides may be prepared by method (4), but are more readily obtained by treatment of the corresponding chlorides with sodium iodide in acetone;[19] the lower members can also be obtained from ω-fluoroalcohols:

(8) $F(CH_2)_nX + NaI \longrightarrow F(CH_2)_nI + NaX$

(9) $6\,F(CH_2)_nOH + 2\,P + 3\,I_2 \longrightarrow 6\,F(CH_2)_nI + 2\,H_3PO_3$

For preparing rare, higher members of the series, unsymmetrical anodic coupling reactions may be used to advantage:

(10) $F(CH_2)_nCOOH + HOOC(CH_2)_mX \longrightarrow F(CH_2)_{n+m}X + 2\,CO_2 + H_2$

For example, 13-fluorotridecyl chloride was obtained from 10-fluorodecanoic acid and 5-chlorovaleric acid. This and other applications of the Kolbe synthesis have been described in an earlier publication.[20]

Details of the preparations are summarized in Tables II and III. The intermediates were obtained commercially or by standard routes: ω,ω'-dihalogenoalkanes were prepared by anodic syntheses,[20] and from the corresponding glycols[21] or cyclic ethers;[22] ω-fluoroalcohols have been described previously.[2]

For the partial fluorination of dihalides using potassium fluoride in ethylene glycol, Hoffmann[7]

TABLE III

OTHER PREPARATIONS OF ω-FLUOROALKYL HALIDES

ω-Fluoroalkyl Halide	Reactant	Method[a]	Yield, %
$F(CH_2)_2Cl$	$F(CH_2)_2OH$	3[b]	71.5
$F(CH_2)_2Br$	$F(CH_2)_2OH$	2	49
$F(CH_2)_2I$	$F(CH_2)_2OSO_2$-$C_6H_4CH_3$	4	66
$F(CH_2)_3Br$	$F(CH_2)_3OH$	2	65
$F(CH_2)_3I$	$F(CH_2)_3Br$	8	64
	$F(CH_2)_3OH$	9	45
$F(CH_2)_4Br$	$F(CH_2)_4OH$	2	63
$F(CH_2)_4I$	$F(CH_2)_4Cl$	8	93
$F(CH_2)_5Cl$	$F(CH_2)_5OH$	3[b]	78
$F(CH_2)_5Br$	$F(CH_2)_5OH$	2	75.5
$F(CH_2)_5I$	$F(CH_2)_5Cl$	8	90.5
$F(CH_2)_6Cl$	$F(CH_2)_6OH$	3[b]	85
$F(CH_2)_6Br$	$F(CH_2)_6OH$	2	85
$F(CH_2)_6I$	$F(CH_2)_6Cl$	8	90
$F(CH_2)_7Cl$	$F(CH_2)_7OH$	3	77
		3[b]	89
$F(CH_2)_7Br$	$F(CH_2)_7OH$	2	75.6
$F(CH_2)_8Cl$	$F(CH_2)_8OH$	3	82
		3[b]	88
$F(CH_2)_9Cl$	$F(CH_2)_9OH$	3[b]	96
$F(CH_2)_{10}Cl$	$F(CH_2)_{10}OH$	3	93
$F(CH_2)_{10}Br$	$F(CH_2)_{10}OH$	2	84
$F(CH_2)_{11}Br$	$F(CH_2)_{11}OH$	2	80
$F(CH_2)_{12}Br$	$F(CH_2)_{12}OH$	2	63
$F(CH_2)_{13}Cl$	$F(CH_2)_9COOH$	10	24.4

[a] Methods of preparation correspond to numbered equations in text. [b] Using pyridine as a condensing agent.

(19) Finkelstein, *Ber.*, **43**, 1528 (1910); Ahmad, Bumpus, and Strong, *J. Am. Chem. Soc.*, **70**, 3391 (1948).

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

(21) Raphael and Sondheimer, *J. Chem. Soc.*, 2100 (1950); Coleman and Bywater, *J. Am. Chem. Soc.*, **66**, 1821 (1944).

(22) Andrus, *Org. Syntheses*, Coll. Vol. **3**, 692 (1955); Fried and Kleene, *J. Am. Chem. Soc.*, **63**, 2691 (1941).

recommends a temperature of 100° for bromides and 130° for chlorides; except in the case of the lower members, no attempt was made to remove continuously the fluorohalides as they were formed. In the present investigation, we have extended the continuous removal to higher members by carrying out the reaction in diethylene glycol under reduced pressure. It can be seen from Table II that the yields are greatly improved, and that the times of the reactions are shortened considerably. The optimum conditions previously described[2] for fluorinations apply similarly in much of this work; it has been found however that a higher concentration of reactants is advisable, approximately 400 g. of diethylene glycol per mole of dihalide being satisfactory.

ω,ω'-Difluoroalkanes, $F(CH_2)_nF$, were obtained as byproducts in most of the partial fluorinations,[7,12] by total fluorination of dichlorides,[12] and by symmetrical anodic coupling of ω-fluorocarboxylic acids.[20] Of those subjected to toxicological examination (see below), 1,4-difluorobutane was prepared by the first method, 1,5-difluoropentane, 1,7-difluoroheptane, and 1,18-difluorooctadecane were obtained by the second method, and 1,8-difluorooctane, 1,10-difluorodecane, 1,12-difluorododecane, 1,14-difluorotetradecane, 1,16-difluorohexadecane, 1,18-difluorooctadecane, and 1,20-difluoroeicosane by the third method. The samples of 1,18-difluorooctadecane obtained by the two different methods were proved to be identical.[20]

PROPERTIES

Chemical. The main value of these derivatives lies in the greater stability of the carbon-fluorine bond relative to that of the other carbon-halogen bonds, making it possible to replace the halogen atom by standard reactions without affecting the fluorine atom. They have thus become valuable synthetic intermediates, from which have been prepared a wide variety of ω-fluorocompounds, including acetylenes, nitriles, nitro-compounds, nitrates, thiocyanates, mercaptans, sulfonate esters, and substituted malonic esters.

ω-Fluoroalkyl halides react with both magnesium and lithium under carefully controlled conditions, forming the corresponding ω-fluoroorganometallic reagents; thus, 6-fluorohexyl chloride, on treatment with magnesium followed by carbon dioxide, formed

TABLE IV

PHYSICAL CONSTANTS OF ω-FLUOROALKYL HALIDES

ω-Fluoroalkyl Halide	Boiling Point °C.	Mm.	n_D^{25}	d_4^{20}
2-Fluoroethyl chloride[a]	53.5–53.8	740	1.3727	
2-Fluoroethyl bromide[b]	70–71	745	1.4236	
2-Fluoroethyl iodide[c]	89–91	740	1.4981	
3-Fluoropropyl chloride[d]	80.5–81.3	740	1.3871	
3-Fluoropropyl bromide[e]	100–101	750	1.4290	
3-Fluoropropyl iodide	127.5–127.8	742	1.4955	
	68–69	95		
4-Fluorobutyl chloride[f]	114.3–114.5	740	1.4020	
4-Fluorobutyl bromide[g]	134.2–134.8	740	1.4370	
4-Fluorobutyl iodide	52.5–53.5	13	1.4937	
5-Fluoroamyl chloride[h]	69.5–70.5	56	1.4109	
	142.8–143.4	735		
5-Fluoroamyl bromide[i]	54.5–55	13	1.4414	
5-Fluoroamyl iodide	71–72	11	1.4912	
6-Fluorohexyl chloride	61.5–62	15	1.4168	1.015
	167	740		
6-Fluorohexyl bromide	67–68	11	1.4435	1.293
6-Fluorohexyl iodide	89–89.5	13	1.4882	1.555
7-Fluoroheptyl chloride	70–71	10	1.4222	0.993
7-Fluoroheptyl bromide	85–86	11	1.4463	
8-Fluorooctyl chloride	87–87.5	10	1.4266	0.978
8-Fluorooctyl bromide	118–120	22.5	1.4484	
9-Fluorononyl chloride	102–102.5	11	1.4301	0.966
10-Fluorodecyl chloride	115–115.5	9	1.4333	0.957
10-Fluorodecyl bromide	131–132	11	1.4512	1.152
11-Fluoroundecyl bromide[j]	95–96	0.6	1.4518	
12-Fluorododecyl bromide	85–86	0.15	1.4524	
13-Fluorotridecyl chloride[k]	160–161	14.5	1.4407	

[a] Hoffmann[7] reports b.p. 53.2° and n_D^{25} 1.3727. [b] Henne and Renoll[13] report b.p. 71.5° and n_D^{25} 1.42261. [c] Henne and Renoll[13] report b.p. 98–102°. [d] Hoffmann[7] reports b.p. 82.5° and $n_D^{27.2}$ 1.3855. [e] Hoffmann[12] reports b.p. 101.4° and n_D^{25} 1.4295. [f] Hoffmann[12] reports b.p. 114.7° and n_D^{23} 1.4025. [g] Hoffmann[7] reports b.p. 134.2° and n_D^{25} 1.4372. [h] Hoffmann[12] reports b.p. 143.2° and n_D^{23} 1.4120. [i] Hoffmann[7] reports b.p. 162° and n_D^{25} 1.4406. [j] Reported previously.[2] [k] Reported previously.[20]

7-fluoroheptanoic acid (64%). The preparation and uses of these derivatives have been outlined briefly.[5,23]

Physical. The physical constants of the ω-fluoroalkyl halides are shown in Table IV. Of the ω,ω'-difluoroalkanes, 1,7-difluoroheptane had b.p. 48° (10 mm.) and n_D^{25} 1.3847; all the others are listed elsewhere.[12,20]

Toxicological. The toxicities of only two members of the ω-fluoroalkyl halide series have been mentioned in the literature. 2-Fluoroethyl chloride is non-toxic;[6] the chlorine atom in this compound was found to be very unreactive, and this fact was correlated with the lack of toxic symptoms, since it was considered unlikely that hydrolysis could occur *in vivo* to form the toxic 2-fluoroethanol. 2-Fluoroethyl bromide is also non-toxic,[6,14] presumably for the same reason. These facts are consistent with the pharmacology of simple alkyl halides; thus, ethyl chloride apparently does not form ethyl alcohol when used as a general anaesthetic,[24] and ethyl iodide is largely recovered unchanged in the urine and respiratory gases when used for testing circulatory rates.[25]

It has become apparent in this work that the halogen atom of the higher ω-fluoroalkyl halides is more labile than that of the 2-fluoroethyl halides. This suggested that the higher members might more readily be hydrolyzed *in vivo* to the corresponding ω-fluoroalcohols. Thus the even members would be expected to be more toxic than the odd members. This is confirmed by the figures presented in Table V.

The chlorides and iodides seem to be rather more toxic than the bromides, and the typical alternation is apparent on ascent of the series. The toxicology of all but the lowest members thus conforms closely to that of the original ω-fluoroalcohol series[2] and this in turn confirms the ready loss of halogen postulated above. It is not unreasonable to extend these results and conclusions to non-fluorinated alkyl halides, thus affording the first concrete evidence for the biological conversion of aliphatic halogen compounds to the corresponding alcohols. This reasoning illustrates a simple and clear-cut method of demonstrating *in vivo* conversions of functional groups, by using the ω-fluorine atom, with its characteristic toxicological properties, as a "tag." Further reference will be made to this method in connection with several other aliphatic series.

Because of the resistance of the carbon-fluorine bond to hydrolysis, it was expected that the ω,ω'-difluoroalkanes, $F(CH_2)_nF$ would be excreted unchanged. The members listed in Table VI were submitted for routine testing and, surprisingly, were found to be toxic.

TABLE V

TOXICITY OF ω-FLUOROALKYL HALIDES

Compound	L.D. 50 for mice (intraperitoneal) mg./kg.
2-Fluoroethyl iodide	28
3-Fluoropropyl bromide	>100
4-Fluorobutyl chloride	1.25
4-Fluorobutyl bromide	8.2
4-Fluorobutyl iodide	5.2
5-Fluoroamyl chloride	32
5-Fluoroamyl iodide	8.5
6-Fluorohexyl chloride	5.8
6-Fluorohexyl bromide	12.8
6-Fluorohexyl iodide	4.5
7-Fluoroheptyl chloride	>100
7-Fluoroheptyl bromide	>100
8-Fluorooctyl chloride	2.3
8-Fluorooctyl bromide	20
9-Fluorononyl chloride	>100
10-Fluorodecyl chloride	5.0
10-Fluorodecyl bromide	20
11-Fluoroundecyl bromide	>100
12-Fluorododecyl bromide	16
13-Fluorotridecyl chloride	40

TABLE VI

TOXICITY OF ω,ω'-DIFLUOROALKANES

Compound	L.D. 50 for mice (Intraperitoneal) mg./kg.
1,4-Difluorobutane	3.4
1,5-Difluoropentane	18
1,7-Difluoroheptane	21.3
1,8-Difluorooctane	1.6
1,10-Difluorodecane	2.15
1,12-Difluorododecane	2.55
1,14-Difluorotetradecane	2.35
1,16-Difluorohexadecane	10.9
1,18-Difluorooctadecane	10
1,20-Difluoroeicosane	10.2
1,18-Dichlorooctadecane	>100

EXPERIMENTAL[26]

The experimental details are subdivided according to the methods described above in equations 1 to 10. The compounds prepared and the individual methods employed are listed in Tables II and III, physical constants in Table IV, and analytical data in Table VII. Representative examples are given below.

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

(24) Kochmann, in Heffter's *Handbuch der Exptl. Pharm.*, 1, 248 (1923).

(25) Blumgart, Gilligan, and Swartz, *J. Clin. Invest.*, 9, 635 (1931).

(26) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J. Results are shown in Table VII. (b) The boiling points are uncorrected. (c) Intermediates which were obtained from commercial sources were purified just before use. (d) Potassium fluoride and glycol solvents were purified as previously described.[2]

TABLE VII

ANALYTICAL DATA

Compound	C		H		Halogen	
	Calc'd	Found	Calc'd	Found	Calc'd	Found
$F(CH_2)_2I$	13.79	14.18	2.30	2.61		
$F(CH_2)_3I$	19.16	19.01	3.19	3.18	I, 67.54	67.15
$F(CH_2)_4I$					I, 63.78	64.08
$F(CH_2)_5I$	27.80	27.64	4.63	4.94		
$F(CH_2)_6Cl$	51.98	51.78	8.66	8.93	Cl, 25.63	25.20
$F(CH_2)_6Br$	39.33	39.08	6.56	6.54	Br, 43.71	43.89
$F(CH_2)_6I$					I, 55.22	55.27
$F(CH_2)_7F$	61.76	61.83	10.29	10.15		
$F(CH_2)_7Cl$	55.09	55.00	9.18	9.28	Cl, 23.28	23.17
$F(CH_2)_7Br$					Br, 40.61	40.20
$F(CH_2)_8Cl$					Cl, 21.32	21.09
$F(CH_2)_8Br$					Br, 37.91	37.80
$F(CH_2)_9Cl$	59.82	59.53	9.97	9.71	Cl, 19.62	19.29
$F(CH_2)_{10}Cl$	61.70	61.93	10.28	10.17	Cl, 18.25	18.03
$F(CH_2)_{10}Br$					Br, 33.44	32.96
$F(CH_2)_{11}Br$					Br, 31.62	31.40
$F(CH_2)_{12}Br$					Br, 30.00	29.62

METHOD (1): PARTIAL FLUORINATION OF ω,ω'-DIHALOGENOALKANES

(*a*). *6-Fluorohexyl chloride.* The apparatus consisted of a 1-liter three-necked flask equipped with a thermometer, a precision-bore stirrer (Hershberg type), and a 25-cm. Vigreux column fitted for vacuum distillation. A mixture of 1,6-dichlorohexane (168 g., 1.08 moles), anhydrous potassium fluoride (96 g., 1.65 moles), and diethylene glycol (400 g.) was heated to 125° and stirred vigorously. The pressure of the system was gradually reduced (*ca.* 90–100 mm.) until a slow steady rate of distillation was produced (about one drop per two seconds). After approximately three hours, distillation stopped even when the temperature was raised to 150° and the pressure reduced to as low as 20 mm. Heating and stirring then were continued for an additional hour at atmospheric pressure. The cold reaction mixture was diluted with 1 liter of water and extracted several times with ether. The distillate and ether extract were combined, washed with 10% sodium carbonate solution, and dried over calcium chloride. After removal of the ether the product was fractionated under reduced pressure. After a small amount of low-boiling forerun, chiefly 1,6-difluorohexane, 72 g. of 6-fluorohexyl chloride were collected. Further distillation gave 25 g. of unchanged 1,6-dichlorohexane, b.p. 82–83° (11 mm.). This represents a yield of 56.5% based on reacted dichloride. The ether extraction may be omitted with only very slight reduction in yield.

(*b*). *5-Fluoroamyl bromide.* Using an apparatus similar to that described in (*a*), a mixture of potassium fluoride (84 g., 1.45 moles), 1,5-dibromopentane (150 g., 0.65 mole), and diethylene glycol (200 g.) was heated to 100°. The pressure of the system was reduced sufficiently to maintain a slow rate of distillation (approx. 13 mm.). After four hours the distillation rate became very slow, and the temperature of the reaction vessel then was raised until unchanged 1,5-dibromopentane distilled. The distillate was dissolved in ether and dried over calcium sulfate. Fractionation of the product yielded 34.2 g. of 5-fluoroamyl bromide and 54 g. of unchanged 1,5-dibromopentane, b.p. 94–97° (11 mm.). Yield based on reacted dibromide is 48.5%.

METHOD (2): TREATMENT OF ω-FLUOROALCOHOLS WITH PHOSPHORUS TRIBROMIDE

6-Fluorohexyl bromide. 6-Fluorohexanol (50 g., 0.416 mole) was added dropwise with stirring to phosphorus tribromide (54 g., 0.20 mole) cooled in an ice-brine bath. When the addition was complete (approx. 30 mins.), the cooling bath was removed and the mixture was allowed to warm to room temperature. After standing for three hours, the reaction was completed by warming in an oil-bath at 120° for an additional hour. When cool, the reaction mixture was poured onto water and extracted with ether. The extracts were washed successively with water, 10% sodium carbonate solution, and water. After drying over calcium chloride, removal of the ether and fractionation of the residue yielded 65 g. (85%) of 6-fluorohexyl bromide.

METHOD (3): TREATMENT OF ω-FLUOROALCOHOLS WITH THIONYL CHLORIDE

This conversion has been carried out both in the presence and absence of a tertiary base. The former method[27] generally proved more satisfactory. In large scale runs, the major portion of the excess thionyl chloride was removed by distillation before isolating the product.

(*a*). *9-Fluorononyl chloride.* Thionyl chloride (38.0 g., 0.32 mole) was added dropwise to a stirred mixture of 9-fluorononanol (24.3 g., 0.15 mole) and pyridine (1 ml.), cooled in an ice-brine bath. When the addition was complete, the cooling bath was removed; after slowly warming to room temperature, the mixture was refluxed on a water-bath for three hours. After standing overnight, the reaction mixture was cooled in an ice-bath while the excess thionyl chloride was decomposed by the addition of water. The fluorohalide was extracted with petroleum ether (30–60°), separated, washed twice with sodium bicarbonate solution and once with water, and then dried over calcium chloride. Fractionation of the product gave 26 g. (96%) of 9-fluorononyl chloride.

(*b*). *10-Fluorodecyl chloride.* 10-Fluorodecanol (65 g., 0.37 mole) was added dropwise with stirring to thionyl chloride (85 g., 0.71 mole). The resultant mixture then was heated under reflux for three hours. After standing overnight the reaction mixture was boiled for an additional 15 hours. Excess thionyl chloride was decomposed by the cautious addition of water. The fluorohalide was extracted with ether, washed with saturated sodium bicarbonate solution and water, and then dried over magnesium sulfate. After removal of the ether, the residue was distilled under reduced pressure to give 67 g. (93%) of 10-fluorodecyl chloride.

(27) Raphael and Sondheimer, *J. Chem. Soc.*, 2100 (1950).

METHOD (4): CLEAVAGE OF SULFONATES WITH POTASSIUM HALIDE

2-Fluoroethyl iodide. A mixture of 2-fluoroethyl *p*-toluenesulfonate[17] (32 g., 0.146 mole), potassium iodide (24 g., 0.15 mole), and water (7.5 ml.) was heated in an oil-bath for 30 min. at 150°. Direct distillation gave impure 2-fluoroethyl iodide contaminated with iodine. The crude product was dissolved in ether, washed successively with sodium thiosulfate solution and water, and dried over calcium chloride. Distillation from freshly prepared silver crystals gave 17 g. (66%) of 2-fluoroethyl iodide.

METHOD (5): CLEAVAGE OF SULFONATES WITH POTASSIUM FLUORIDE

This procedure has been described elsewhere.[10]

METHOD (8): TREATMENT OF ω-FLUOROALKYL CHLORIDES WITH SODIUM IODIDE

6-Fluorohexyl iodide. Sodium iodide (52 g., 0.35 mole) was dissolved in boiling acetone (75 ml.) and 6-fluorohexyl chloride (16 g., 0.12 mole) was added dropwise over the next hour. The resultant mixture then was heated under reflux for 18 hours. After cooling, the reaction mixture was diluted with water and the organic layer was extracted with ether. The extract was washed successively with water, sodium bicarbonate solution, and water, and then dried over calcium chloride. Concentration of the dried extract and distillation of the residue from freshly prepared silver crystals gave 24 g. (90%) of 6-fluorohexyl iodide.

METHOD (9): TREATMENT OF ω-FLUOROALCOHOLS WITH PHOSPHORUS AND IODINE

3-Fluoropropyl iodide. 3-Fluoropropanol (30 g., 0.375 mole) and red phosphorus (5.2 g., 0.17 mole) were heated in an apparatus which allowed the gradual addition of iodine (48 g., 0.375 mole) by its being dissolved and carried down with the refluxing liquid.[28] After all the iodine had been added, the crude fluoroiodide was isolated by pouring into 1 liter of water and separating the organic layer, which was purified by washing with 10% sodium thiosulfate solution until colorless, and then with water. Finally, it was dried over calcium chloride and fractionally distilled from freshly prepared silver crystals. 3-Fluoropropyl iodide was obtained as a colorless liquid (31.7 g., 45%).

METHOD (10): UNSYMMETRICAL ANODIC COUPLING REACTIONS

This procedure has been described elsewhere.[20]

Acknowledgments. The work described herein was carried out under Contract (DRB X-24) with the Defence Research Board of Canada, to whom grateful acknowledgment is made for financial assistance, and for permission to publish this work. The authors wish also to express their indebtedness to the Research Council of Ontario for a scholarship (W. C. H.) and to the National Research Council of Canada for a Studentship and Fellowship (W. C. H.); to Drs. M. K. McPhail and F. C. G. Hoskin and Mr. P. A. Adie, Suffield Experimental Station, Ralston, Alberta, and Dr. J. M. Parker, Defence Research Medical Laboratories, Toronto for carrying out the toxicity determinations; to E. I. du Pont de Nemours and Co. for generous gifts of 1,4-dichlorobutane, tetrahydrofuran, and tetrahydropyran; and to Messrs. W. J. Cott, P. Huston, D. Kovachic, J. E. Millington, J. J. Norman, J. W. B. Reesor, J. C. Schneider, and R. G. Woolford for valuable contributions to this investigation.

LONDON, ONTARIO

(28) See, for example, the preparation of *n*-butyl iodide. Vogel, *A Textbook of Practical Organic Chemistry*, Longmans, Green and Co., London, 1948, p. 284.