ALIPHATIC VICINAL FLUOROBROMIDES

SOME PREPARATIONS AND REACTIONS[1]

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Received November 16, 1964

ABSTRACT

The addition of "BrF", using *N*-bromoamides in anhydrous hydrogen fluoride, to a number of aliphatic alkenes has been studied. As expected, the bromine atom in the resultant vicinal fluorobromides exhibited relatively low reactivity in nucleophilic and hydrogenolytic reactions.

The bromine monofluoride addition reaction, first described by Bowers (2, 3, 4), has been employed mainly in the synthesis of fluorinated steroids. Its application to aliphatic alkenes was undertaken here partly to extend the scope of the reaction and partly to obtain the resultant vicinal fluorobromides as intermediates in other syntheses; of particular interest was their potential use in the synthesis of α-monofluoroalkanoic acids (5). While this work was in progress, parallel studies using perchloryl fluoride were continuing, with α-monofluoroalkanoic acids again as the main goal (5). The two methods are complementary, in that they permit the introduction of the fluorine atom at centers of low electron density (bromonium ion) and high electron density (carbanion) respectively. Prior to this work, the only common aliphatic vicinal fluorohalides were those derived from ethane. Of these, 1-bromo-2-fluoroethane had been reported by Schrader (6) to be formed by the direct addition of "BrF" (using a mixture of bromine and fluorine) to ethylene; the present work may thus be considered as a refinement of this original procedure.

$$RCH{=}CH_2 + CH_3C\overset{+}{O}NH_2Br \rightarrow RC\overset{Br}{\overset{/+\backslash}{H}}{-}{-}CH_2 + CH_3CONH_2$$

I

$$RC\overset{Br}{\overset{/+\backslash}{H}}{-}{-}CH_2 + HF \rightarrow RCHFCH_2Br + H^+$$

1-Alkenes of medium chain length on treatment with a molar quantity of *N*-bromoacetamide and excess anhydrous hydrogen fluoride in ether gave the expected products in good yield (70–80%), with small amounts of isomeric 2-bromo-1-fluoroalkanes. The structures of the major products were shown to be the 1-bromo-2-fluoroalkanes by nuclear magnetic resonance (n.m.r.) spectroscopy and by their conversion in high yield to the corresponding α-monofluoroalkanoic acids (5). The minor products were isolated in only a few instances (for example, in the addition to allyl bromide); they proved to be the anti-Markovnikov isomers. The minor product was usually not removed from the mixture, because it was destroyed or removed in many of the subsequent reactions. Yields are shown in Table I.

[1]*This paper was presented in part at the Second International Symposium on Fluorine Chemistry, Estes Park, Colorado, July 17–20, 1962 (1).*
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The most satisfactory general technique involved the addition of *N*-bromoacetamide and the alkene, alternately and in small portions, to a cooled (−80°) solution of anhydrous hydrogen fluoride in ether. Some variations were examined briefly. (*a*) *The nature of the bromine source.* Three reagents were tried, *N*-bromoacetamide (NBA), 1,3-dibromo-5,5-dimethylhydantoin (DBH), and 1-bromo-3,5,5-trimethylhydantoin (BTH). All gave approximately the same yields. However, the higher solubility of the hydantoins in the reaction medium permitted a simpler method of adding the reagents. (*b*) *The addition of reagents.* NBA was insoluble in the cold ether solution, but DBH and BTH were sufficiently soluble to be added in one portion prior to the dropwise addition of the alkene. The yields were comparable when the alkene was added in its entirety and the brominating agent was added in portions. Moreover, the yield was only slightly diminished when both the brominating agent and the alkene were added in one portion at the start of the reaction. In short, for maximum yield, alternate portionwise addition is recommended, whereas for maximum simplicity, addition of all reagents to the ether solution is preferred. (*c*) *Solvent.* Ether was found to be satisfactory in most instances. For ethylene, however, methylene dichloride, at a reaction temperature of −30°, proved to be the most effective solvent. 1-Butene gave the fluorobromide in chloroform or in ether–chloroform. In general, a mixture of solvents (such as an ether and a halogenoalkane) is likely to be most generally satisfactory.

The alkene component was varied in order to examine the versatility of the reaction. (*a*) Gases were found to react normally, but in lower yield; ethylene, propylene, and 1-butene thus gave the expected products in 25–50% yield. (*b*) Higher molecular weight alkenes could also be used; 1-decene gave a 78% yield of 1-bromo-2-fluorodecane. 1-Octadecene reacted more slowly, because of its low solubility in the reaction medium; the resultant mixture of product and starting material was used directly in subsequent steps. (*c*) Branched alkenes reacted in lower yield; for example, 2-ethyl-1-butene gave 1-bromo-2-fluoro-2-ethylbutane (56%). (*d*) The highly reactive alkene styrene gave a poor (25%) yield of the adduct by the usual process; much polymeric material was formed. When some pyridine was added to increase the concentration of fluoride ion, the yield of styrene fluorobromide was more than doubled. The designation of the product as 1-bromo-2-fluoro-2-phenylethane is consistent with the observations of Buckles and Knaack (7) on the mode of addition of iodine monochloride to styrene. Stilbene also reacted normally in low yield. (*e*) The presence of other functional groups seemed to have no effect on the addition reaction; for example, methyl 10-undecenoate gave methyl 11-bromo-10-fluoroundecanoate in 71% yield. The addition to acrylates, to allyl esters, and to bridged bicyclic systems (with concomitant Wagner–Meerwein rearrangement) will be described in later communications.

Allyl bromide was expected to form 1,3-dibromo-2-fluoropropane (II) as the predominant product by the usual Markovnikov addition mechanism. It was found, however, that the anti-Markovnikov adduct 1,2-dibromo-3-fluoropropane (III) was formed in 32% yield, while the yield of the Markovnikov adduct II was only 22%.

$BrCH_2CHFCH_2Br$ $BrCH_2CHBrCH_2F$ $[CH_2{-}CH{-}CH_2]^+$ (Br bridging)

II III IV

Anomalous product ratios have been observed by de la Mare and co-workers in studies of the addition of hypochlorous acid to allyl halides (8, 9, 10). The products in the present

work may be explained by postulating that the reaction proceeds through the symmetrical bromonium ion IV (8). The major product would then arise from nucleophilic attack by fluoride ion on the more plentiful, exposed primary carbon atoms. Simple steric effects may also be involved.

Some side reactions were observed. Ether formation occurred in some reactions. For example, a bromoethoxyheptane was isolated from the addition reaction with 1-heptene; this is probably formed by partial hydrolysis of solvent ether to ethanol, which in turn reacts with the bromonium ion intermediate (I). Other side reactions included the addition of the elements of *N*-bromoacetamide to the double bond and proton elimination from the bromonium ion intermediate; both these reactions were observed principally in the addition to bridged bicyclic systems, and will be described in a later paper.

The aliphatic vicinal fluorobromides are colorless, mobile liquids possessing odors similar to those of the corresponding alkyl bromides. They are nontoxic, indicating that they are not metabolized to fluoroacetic acid; for example, both 1-iodo-2-fluorohexane and 2-fluoro-1-hexanol had $LD_{50} > 107$ mg/kg (intraperitoneal injection into mice). They boil at a higher temperature, have greater densities, and have lower refractive indices than the corresponding alkyl bromides (Table II). They normally exhibit a C—F band in the infrared at 1 010 – 1 016 cm^{-1}. Most of the vicinal fluorobromides are stable when stored in sealed glass ampoules at room temperature, but some, for example styrene fluorobromide and *trans*-1-bromo-2-fluorocyclohexane, showed a marked tendency to decompose; this could be due to autocatalysis by small amounts of hydrogen fluoride formed during the sealing process.

The reactivity of 1-bromo-2-fluoroalkanes towards nucleophilic reagents was expected to be less than that of *n*-alkyl bromides; thus, Hine (11, 12) has found that 1-bromo-2-fluoroethane reacts only one-eighth as rapidly as ethyl bromide with the thiophenoxide ion. In a series of scouting reactions, it was found that the 1-bromo-2-fluoroalkanes underwent nucleophilic substitutions under conditions which were more vigorous than those one might normally use for *n*-alkyl bromides. By this means one or more members (Table II) of the following classes of 2-fluoroalkyl derivatives were prepared (reagents in brackets): acetates (sodium acetate plus sodium iodide in dry dimethylformamide), azides (sodium azide in aqueous dimethylformamide), iodides (sodium iodide in acetone), formates (sodium formate plus sodium iodide in dry dimethylformamide), nitrates (silver nitrate in acetonitrile), thiocyanates (potassium thiocyanate in ethanol), *p*-nitrobenzoates (lithium *p*-nitrobenzoate in dry dimethylformamide), and tosylates (silver tosylate in acetonitrile). When treated with sodium cyanide in dimethyl sulfoxide, 1-bromo-2-fluorohexane gave 1,2-dicyanohexane rather than the expected 3-fluoroheptanonitrile; the analogous reaction of 1-bromo-2-fluoroethane to yield succinodinitrile has been reported by Mirosevic-Sorgo and Saunders (13). 1-Iodo-2-fluorohexane did not alkylate the dimethyl malonate anion. In a study of the reductive elimination of 1,2-dihalides with lithium aluminium hydride, King and Pews (14) have reported that *erythro*-1-bromo-2-fluoro-1,2-diphenylethane formed *trans*-stilbene in 86% yield, whereas *trans*-1-bromo-2-fluorocyclohexane (3) formed fluorocyclohexane in 45% yield.

The acetates (and, to a lesser extent, the nitrates and formates) were important intermediates in a general route to α-monofluoroalkanoic acids; this is probably the most valuable application of the work (5). The nitrates were readily hydrogenolyzed using platinum in ethanol to the corresponding 2-fluoro-1-alkanols, $RCHFCH_2OH$; this affords a convenient route to these hitherto inaccessible fluoroalcohols. (Most common procedures, such as opening of epoxides with hydrogen fluoride (15), yield the isomeric

TABLE I

Yields of vicinal fluorobromides

Alkene	Scale* (moles)	Solvent†	Molar ratio HF:alkene	% HF in solvent (w/w)	Product‡	Yield§ (%)
$CH_2{=}CH_2$	0.72	CH_2Cl_2	5.0	21	FCH_2CH_2Br	23‖
$CH_3CH{=}CH_2$	1.00*	CH_2Cl_2	5.0	18	CH_3CHFCH_2Br	38‖
$CH_3CH_2CH{=}CH_2$	0.35	$CHCl_3$ (68) – ether (32)	5.6	18	$CH_3CH_2CHFCH_2Br$	55‖
$CH_3(CH_2)_3CH{=}CH_2$	0.50	Et_2O	12.8	43	$CH_3(CH_2)_3CHFCH_2Br$	79
$CH_3(CH_2)_4CH{=}CH_2$	0.79	Et_2O	9.4	41	$CH_3(CH_2)_4CHFCH_2Br$	77
$CH_3(CH_2)_5CH{=}CH_2$	0.75	Et_2O	9.3	40	$CH_3(CH_2)_5CHFCH_2Br$	70
$CH_3(CH_2)_7CH{=}CH_2$	0.69	Et_2O	10.1	40	$CH_3(CH_2)_7CHFCH_2Br$	78
$CH_3(CH_2)_{15}CH{=}CH_2$	0.17	Et_2O (62) – dioxane (38)	33.6	12	$CH_3(CH_2)_{15}CHFCH_2Br$	—¶
$CH_3CH_2CEt{=}CH_2$	0.40	Et_2O	10.6	38	$CH_3CH_2CEtFCH_2Br$	56
$C_6H_5CH{=}CH_2$	0.21	Et_2O	22.7	40	$C_6H_5CHFCH_2Br$	25
$C_6H_5CH{=}CH_2$	0.42	Et_2O (79) – pyridine (21)**	13.4	20	$C_6H_5CHFCH_2Br$	68
$C_6H_5CH{=}CHC_6H_5$	0.02	THF	45.0	30	$C_6H_5CHFCHBrC_6H_5$	25
$CH_2{=}CHCH_2Br$	0.25	Et_2O	7.8	35	$BrCH_2CHFCH_2Br$ (II)	22
					$FCH_2CHBrCH_2Br$ (III)	32
$CH_2{=}CH(CH_2)_8COOMe$	0.35*	$CHCl_3$	7.2	14	$BrCH_2CHF(CH_2)_8COOMe$	72

*The figures shown are for the alkenes; the brominating agent was used in approximately equimolar quantities. *N*-Bromoacetamide was used in all reactions except those of propylene and methyl 10-undecenoate, when 1,3-dibromo-5,5-dimethylhydantoin was the bromine source.
†Ether was the most commonly used solvent, either alone or in combination.
‡The compound listed is the major product.
§The yield represents the total purified mixture of the two fluorobromide isomers; the minor (anti-Markovnikov) isomer amounted to some 3–8% of the total sample (g.l.c. analyses).
‖Yield is based on brominating agent.
¶Crude mixture of unreacted alkene and fluorobromide was used without purification.
**A total of 1.5 moles of pyridine was used (see Experimental).

1-fluoro-2-alkanols, $RCH(OH)CH_2F$.) An even simpler, direct procedure for converting the 1-bromo-2-fluoroalkanes to 2-fluoro-1-alkanols involved the use of sodium formate in hot aqueous dimethylformamide; thus, 2-fluoro-1-hexanol of high purity was obtained in 75% yield.

Because the crude 2-fluorooctadecyl acetate was a greasy, low-melting solid, a more satisfactory crystalline derivative was required for analysis and for conversion to 2-fluorooctadecanoic acid. The *p*-nitrobenzoate was therefore prepared in fair yield. Since nitrobenzoate esters are known to be resistant to acid hydrolysis (16), the *p*-aminobenzoate was prepared in excellent yield using Adams' catalyst.

Vicinal fluorobromides and fluoroiodides were entirely resistant to hydrogenolysis at room temperature and atmospheric pressure using platinum as catalyst; under the same conditions, vicinal dibromides were readily dehalogenated to the corresponding alkanes. For example, *trans*-1-bromo-2-fluorocyclohexane (3) failed to react under conditions that resulted in the ready conversion of *trans*-1,2-dibromocyclohexane to cyclohexane. This difference in reactivity was used to isolate pure 1,3-dibromo-2-fluoropropane (II) from its mixture with 1,2-dibromo-3-fluoropropane (III); the latter, containing a vicinal dibromide grouping, was destroyed by hydrogenation whereas the former was recovered unchanged. The facile hydrogenolysis of benzylic fluorides is well known; even the relatively stable *gem*-difluoro grouping may be reduced if it lies adjacent to a benzene ring (17). Consequently hydrogenolysis of 2-fluoro-2-phenylethyl nitrate yielded only 2-phenylethanol; similarly, styrene fluorobromide gave ethylbenzene. In this latter case, the β-fluorine atom cannot exert its "protecting" action over the bromine atom because, being labile itself, it is easily removed.

EXPERIMENTAL

Physical constants and analytical data for all new compounds are given in Table II. The preparations described below represent typical examples of each procedure; obvious variations for obtaining different members have not been included. Melting points (uncorrected) were determined on a Kofler hot stage, and densities with a Fisher-Davidson gravitometer. The nuclear magnetic resonance spectra were obtained with a Varian DP-60 spectrometer. Infrared spectra were obtained with Beckman IR-7 and IR-5 infrared spectrophotometers. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, 77, N.Y. Most of the alkenes were purchased from Humphrey-Wilkinson, Inc., Devine Street, North Haven, Conn. Other reactants were obtained from standard commercial sources. Fractionations were carried out using a 23-plate platinum-plated spinning-band column.

A. Preparation of Vicinal Fluorobromides

1-Bromo-2-fluorohexane

Anhydrous hydrogen fluoride (129.7 g, 6.49 moles) was condensed into a 500 ml polythene bottle cooled in dry ice. Cold (−80°) dry ether (240 ml) was added with magnetic stirring. *N*-Bromoacetamide (69.0 g, 0.50 mole) and 1-hexene (42.5 g, 0.505 mole) were added portionwise and alternately over 27 min, with cooling (−80°) and stirring. The NBA dissolved as it was added. The mixture was stirred for 2 h at −80° and then was allowed to stand overnight at this temperature. The resultant solution was neutralized by being poured slowly into a mixture of sodium carbonate (690 g), water (1 200 ml), ice (500 g), and ether (300 ml). The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, treated with nitrous acid to destroy residual acetamide, and then washed with aqueous sodium carbonate and with water until neutral. After drying ($MgSO_4$) and removal of the ether, the resultant amber-colored liquid was fractionated to yield 71.8 g (79%) of 1-bromo-2-fluorohexane. Gas–liquid chromatography (g.l.c.) analysis (DEGS column, 158°) indicated 95 mole % of the main product and 5 mole % of 2-bromo-1-fluorohexane. The infrared spectrum ($CHCl_3$) showed a C—F band at 1 010 and 1 124 cm^{-1}. The n.m.r. spectrum (CCl_4) indicated a $—CH_2Br$ group (doublet of doublets centered at 3.39 p.p.m., J_{HF} 17.4 c/s, J_{HH} 5.6 c/s) and a −CHF group (two widely separated multiplets centered at 4.55 p.p.m., J_{HF} 46.8 c/s).

Variations in Procedure

1,3-Dibromo-5,5-dimethylhydantoin (DBH) and 1-bromo-3,5,5-trimethylhydantoin (BTH) gave results similar to those obtained with NBA. The three following variations in procedure (using DBH as the Br source) were simpler than the above portionwise addition, but gave lower yields.

TABLE II

Physical constants and analytical results

Compound	Formula	Boiling point (°C)	Boiling point (mm)	n_D^{25} or m.p.(°C)	d_4^{20}	MR_D Estimated	MR_D Found	Analytical results: C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	Other (%) Calcd.	Other (%) Found
1. Fluorobromides													
1-Bromo-2-fluoroethane*	FCH_2CH_2Br	71.5	754	1.4227	1.668	18.94	19.35						
1-Bromo-2-fluoropropane	CH_3CHFCH_2Br	88.5	740	1.4213	1.506	23.59	23.73	25.56	25.71	4.29	4.11		
1-Bromo-2-fluorobutane	$CH_3CH_2CHFCH_2Br$	113	758	1.4288	1.410	28.24	28.40	30.99	30.97	5.20	5.17	Br, 51.55	Br, 51.43
1-Bromo-2-fluorohexane	$CH_3(CH_2)_3CHFCH_2Br$	62	18	1.4368	1.287	37.44	37.40	39.36	39.57	6.61	6.64		
1-Bromo-2-fluoroheptane	$CH_3(CH_2)_4CHFCH_2Br$	77	18	1.4395	1.238	42.05	42.09	42.65	42.89	7.16	7.15		
1-Bromo-2-fluorooctane	$CH_3(CH_2)_5CHFCH_2Br$	90	16	1.4423	1.198	46.75	46.80	45.51	45.72	7.64	7.66		
1-Bromo-2-fluorodecane	$CH_3(CH_2)_7CHFCH_2Br$	70	0.72	1.4467	1.136	56.19	56.44	50.22	50.36	8.43	8.48		
1-Bromo-2-fluoro-2-ethylbutane	$CH_3CH_2CEtFCH_2Br$	38	11	1.4391	1.293	37.44	37.40	39.36	39.52	6.61	6.71		
1-Bromo-2-fluoro-2-phenylethane	$C_6H_5CHFCH_2Br$	53	0.05	1.5411	1.468	43.64	43.60	47.32	47.45	3.97	3.98		
1-Bromo-2-fluoro-1,2-diphenylethane	$C_6H_5CHFCHBrC_6H_5$	—	—	106.5–107.5	—	—	—	60.23	60.44	4.33	4.53	Br, 28.63	Br, 28.65
1,3-Dibromo-2-fluoropropane(II)	$BrCH_2CHFCH_2Br$	96	74	1.5026	2.083	31.20	31.20	16.38	16.71	2.29	2.40		
1,2-Dibromo-3-fluoropropane(III)†	$FCH_2CHBrCH_2Br$	—	—	1.5097	—	—	—	16.38	16.64	2.29	2.40	Br, 72.68	Br, 72.44
Methyl 11-bromo-10-fluoroundecanoate	$BrCH_2CHF(CH_2)_8COOMe$	120	0.30	1.4587	1.217	67.01	66.88	48.49	48.57	7.46	7.35	Br, 26.89	Br, 26.73
2. Fluorinated products obtained from fluorobromides													
2-Fluoroethyl acetate‡	FCH_2CH_2OAc	118	745	1.3756	1.086	22.11	22.51						
2-Fluoropropyl acetate	CH_3CHFCH_2OAc	128.5	755	1.3806	1.029	26.76	27.07	49.99	50.22	7.55	7.51		
2-Fluorobutyl acetate	$CH_3CH_2CHFCH_2OAc$	147	761	1.3893	0.998	31.41	31.87	53.72	53.67	8.27	8.15		
2-Fluorohexyl acetate	$CH_3(CH_2)_3CHFCH_2OAc$	74	13	1.4034	0.970	40.51	41.02	59.24	59.46	9.32	9.21		
2-Fluoroheptyl acetate	$CH_3(CH_2)_4CHFCH_2OAc$	87	11	1.4086	0.958	45.20	45.63	61.33	61.51	9.73	9.64		
2-Fluorooctyl acetate	$CH_3(CH_2)_5CHFCH_2OAc$	99	11	1.4134	0.948	49.91	50.30	63.13	62.91	10.07	10.03		

TABLE II (*Concluded*)

Compound	Formula	Boiling point (°C)	Boiling point (mm)	n_D^{25} or m.p.(°C)	d_4^{20}	MR_D Estimated	MR_D Found	Analytical results: C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	Other (%) Calcd.	Other (%) Found
2-Fluorodecyl acetate	$CH_3(CH_2)_7CHFCH_2OAc$	75	0.5	1.4210	0.932	59.55	59.65	66.02	66.15	10.62	10.78		
Methyl 11-acetoxy-10-fluoroundecanoate	$AcOCH_2CHF(CH_2)_8COOMe$	125	0.25	1.4383	1.029	70.19	70.40	60.85	61.01	9.12	9.24		
2-Fluoro-1-hexanol	$CH_3(CH_2)_3CHFCH_2OH$	66	14	1.4065	0.946	31.39	31.37	59.97	59.81	10.90	10.75		
2-Fluoro-1-heptanol	$CH_3(CH_2)_4CHFCH_2OH$	77	8	1.4135	0.932	36.04	36.10	62.65	62.90	11.27	11.28		
2-Fluorohexyl azide	$CH_3(CH_2)_3CHFCH_2N_3$	93	52	1.4248	0.984	37.40	37.88	49.63	49.92	8.27	8.34	N, 28.94	N, 28.80
2-Fluorohexyl iodide	$CH_3(CH_2)_3CHFCH_2I$	75	16	1.4788	1.531	42.62	42.65	31.32	31.56	5.26	5.22	I, 55.16	I, 55.47
2-Fluorodecyl iodide	$CH_3(CH_2)_7CHFCH_2I$	67	0.1	1.4754	1.323	61.12	61.32	41.97	42.00	7.05	6.93		
2-Fluorohexyl formate	$CH_3(CH_2)_3CHFCH_2OCHO$	81	27	1.4022	0.996	36.00	36.40	56.74	57.00	8.78	8.94		
2-Fluoroheptyl formate	$CH_3(CH_2)_4CHFCH_2OCHO$	78	9	1.4082	0.977	40.58	40.71	59.24	59.49	9.32	9.22		
2-Fluorohexyl nitrate	$CH_3(CH_2)_3CHFCH_2ONO_2$	83	14.5	1.4130	1.100	37.86	37.63	43.63	43.50	7.33	7.37	N, 8.48	N, 8.39
2-Fluoro-2-phenylethyl nitrate	$C_6H_6CHFCH_2ONO_2$	56	0.05	1.5030	1.263	43.80	43.50	51.89	52.10	4.35	4.57	N, 7.57	N, 7.60
2-Fluorohexyl thiocyanate§	$CH_3(CH_2)_3CHFCH_2SCN$	71	0.4	1.4563	1.040	42.19	42.32	52.14	52.28	7.50	7.41	N, 8.69	N, 8.83
2-Fluorooctadecyl *p*-nitrobenzoate	$CH_3(CH_2)_{16}CHFCH_2OCOC_6H_4NO_2$	—	—	68–70	—	—	—	68.62	68.70	9.21	9.35		
2-Fluorooctadecyl *p*-aminobenzoate	$CH_3(CH_2)_{16}CHFCH_2OCOC_6H_4NH_2$	—	—	87–89	—	—	—	73.66	73.63	10.39	10.39		
1,3-Bistosyloxy-2-fluoropropane‖	$TsOCH_2CHFCH_2OTs$	—	—	111–112	—	—	—	50.73	50.61	4.76	4.66	S, 15.93	S, 16.11
3. Miscellaneous compounds													
1,2-Dicyanohexane	$CH_3(CH_2)_3CH(CN)CH_2CN$	90	0.12	1.4380	0.925	39.13	38.78	70.54	70.45	8.88	8.74	N, 20.57	N, 20.57
1-Bromo-2-ethoxyheptane	$CH_3(CH_2)_4CH(OEt)CH_2Br$	38	0.17	1.4483	1.122	53.35	53.48	48.44	48.63	8.58	8.77		

*Pattison and Howell (20) report b.p. 70–71° at 745 mm, n_D^{25} 1.4236.
†Hoffmann (18) reports n_D^{23} 1.5092.
‡Millington and Pattison (21) report b.p. 116–117.5° at 740 mm, n_D^{25} 1.3784.
§Moderately toxic: LD_{50} 26.6 mg/kg (95% fiducial limits: 19.4–36.6 mg/kg) by intraperitoneal injection into mice.
‖Taylor and Kent (19) report m.p. 109°. The compound was shown to be nontoxic (LD_{50} > 100 mg/kg by intraperitoneal injection into mice).

(a) Alkene added dropwise.—Using 1-hexene (14.7 g, 0.175 mole), DBH (25.0 g, 0.0875 mole), hydrogen fluoride (45.0 g, 2.25 moles) in ether (50 ml), and carbon tetrachloride (50 ml), the alkene was added dropwise to the vigorously stirred mixture of the other components at −30° over 90 min. Yield: 64%.

(b) DBH added portionwise.—Using the same quantities as in (*a*), the DBH was added in 10 portions to the vigorously stirred mixture of the other components at −30° over 90 min. Yield: 66%.

(c) All reactants added together.—All the above reactants were mixed at the start of the reaction and were stirred for 4 h at −30°. Yield: 64%.

Variations in Alkene Component: Representative Procedures

(a) Ethylene.—Ethylene (20.2 g, 0.72 mole) was passed slowly through a stirred mixture of NBA (50.0 g, 0.36 mole), hydrogen fluoride (72.0 g, 3.6 moles), and methylene chloride (200 ml) at −40° to −20° for 5 h. The temperature should not rise above −20° before the neutralization step. Yield of 1-bromo-2-fluoroethane: 23%. Use of ether as solvent or too high a temperature before neutralization results in a negligible yield of product. A reaction using double quantities of reactants gave the same overall yield (23%).

(b) 1-Butene.—1-Butene (25.0 g, 0.45 mole) was passed into a stirred mixture of NBA (48.0 g, 0.35 mole), hydrogen fluoride (50.0 g, 2.5 moles) in chloroform (100 ml) and ether (100 ml) at −60° to −30° for 3.5 h. Yield of 1-bromo-2-fluorobutane: 55%.

(c) 1-Octadecene.—To anhydrous hydrogen fluoride (117 g, 5.85 moles), ether (725 ml), and dioxane (300 ml) in a half-gallon polythene bottle were added 1-octadecene (44 g, 0.174 mole) and NBA (23.1 g, 0.168 mole) alternately and in small portions over 15 min at −80°. The alkene solidified and floated on the surface; even at 0° it had not all dissolved. The tightly capped bottle was placed in a refrigerator for 17 h, at the end of which time the mixture was colorless and homogeneous. The usual isolation procedure gave the crude bromide as a greasy, pale-yellow solid (60.4 g) which was used directly without purification.

(d) 2-Ethyl-1-butene.—1-Bromo-2-fluoro-2-ethylbutane was prepared in the usual way from 2-ethyl-1-butene (34.0 g, 0.40 mole), NBA (57.5 g, 0.42 mole), anhydrous hydrogen fluoride (86.0 g, 4.30 moles) in ether (200 ml). The mixture was neutralized with potassium bicarbonate (208 g) and potassium carbonate (330 g) to minimize the risk of elimination from the tertiary fluoride. Treatment with nitrous acid removed traces of acetamide. Yield of fluorobromide: 56%.

(e) Styrene.—The usual method gave only 25% of the desired product; much polymeric material was formed. The following modified procedure gave a yield of 68%. In a half-gallon polythene bottle were placed anhydrous hydrogen fluoride (113 g, 5.65 moles) and ether (340 ml). With cooling (−80°) and magnetic stirring, a solution of pyridine (120.5 g, 1.5 moles) in ether (300 ml) was slowly added. The resultant pyridine hydrofluoride crystallized at −80° making magnetic stirring impossible. The mixture was stirred vigorously out of the cooling bath, and styrene (44 g, 0.42 mole) and NBA (59.5 g, 0.43 mole) were added alternately over 30 min. The mixture was cooled to −80° for 1 h and refrigerated at 8° overnight. Isolation and purification gave the required product (68%).

(f) trans-Stilbene.—The reaction was carried out in the usual way, using tetrahydrofuran as solvent. The product was isolated from the neutralized mixture by extraction with chloroform. Removal of the solvent and evaporation of the residue at 100° at 0.1 mm gave colorless needles. These were dissolved in benzene and chromatographed on silica gel. The first fraction on evaporation gave an oil which solidified. Recrystallization from 60–80° petroleum ether gave colorless needles of the pure product (25%); no C=C stretching vibration (ca. 1 600 cm^{-1}) or *trans* out-of-plane deformation (960 cm^{-1}) was observed in the infrared.

(g) Allyl bromide.—The reaction was carried out in the usual manner from 30.4 g (0.25 mole) of allyl bromide; reaction did not occur at −80° but was complete in 25 min at −20°. Further cooling and stirring, followed by isolation and fractionation gave 31.5 g of a colorless liquid of b.p. 69–73° at 3 mm. Gas–liquid chromatographic analysis on a Perkin–Elmer Vapor Fractometer (Model 134), using a polypropylene glycol 550 analytical column, showed that this liquid consisted of two major components (94% of total), both of which were shown to be dibromofluoropropanes by elemental analysis and molecular refractivity of the mixture (MR_D 31.38 cc/mole, estimated 31.20 cc/mole). Gas chromatography at 120°, with a flow rate of 80 ml/min of helium, gave retention times of 20 and 26 min and allowed collection of the pure components; to obtain satisfactory resolution, no more than 30 μl of liquid were injected at any one time. The pure components had n_D^{25} 1.5097 and n_D^{25} 1.5026 respectively, corresponding to 1,2-dibromo-3-fluoropropane (III) and 1,3-dibromo-2-fluoropropane (II); Hoffmann (18) reports n_D^{23} 1.5092 for III. Pure II was isolated in larger amounts by hydrogenolytic removal of III from the mixture of II and III, followed by fractionation (see below); the formation of the bis-tosyloxy derivative (q.v.) confirms the presence of II in the original mixture. The overall yields of II and III were 22% and 32% respectively.

(h) Methyl 10-undecenoate.—The ester (69.3 g, 0.35 mole) was added in portions over 10 min to a stirred mixture of DBH (50 g, 0.175 mole), anhydrous hydrogen fluoride (50 g, 2.5 moles), and chloroform (200 ml) at −55°. The mixture was stirred at −40° for a further 3 h. Isolation and fractionation gave the pure saturated ester (72%). An identical yield was obtained using NBA (49 g, 0.35 mole) in chloroform (200 ml) and ether (100 ml).

Side Reactions

The principal side reaction occurring in the addition to simple alkenes involved the formation of ethers (see Discussion). In the preparation of 1-bromo-2-fluoroheptane, a higher boiling fraction was obtained,

which was purified by preparative gas chromatography (Nester and Faust Prepko at 210° using a 1 in. × 6 ft column of 20% DEGS on 60/80 mesh firebrick with helium (600 ml/min) as carrier); the fraction (ca. 2 g) eluting in 1.7 min was distilled through a spinning-band column to give a bromoethoxyheptane. Its infrared spectrum (CCl_4) was very simple, the main feature being a strong band at 1 106 cm^{-1} (C—O stretch). The n.m.r. spectrum was too complex to permit an assignment of the location of the bromine and ethoxy groups.

B. Reactions of Vicinal Fluorobromides

2-Fluoro-1-hexanol

A mixture of 1-bromo-2-fluorohexane (8.0 g, 43.7 mmoles), sodium formate (5.0 g, 73.5 mmoles), dimethylformamide (50 ml), water (16.6 ml), and tetrahydrofuran (25 ml) was heated under reflux at 130° for 31 h. The cooled mixture was diluted with water (100 ml) and extracted with ether. The extracts were washed with water, with aqueous sodium bicarbonate, and with water again. The dried (Na_2SO_4) solvent-free product gave an infrared spectrum which showed the presence of some formate ester. Hence the product was hydrolyzed by refluxing at 105° for 19 h with water (8 g). Isolation in the usual way gave the pure fluoroalcohol (3.95 g, 75%).

2-Fluorohexyl Acetate

1-Bromo-2-fluorohexane (10.0 g, 54.6 mmoles) was stirred and refluxed with dry sodium acetate (7.0 g, 84.4 mmoles) and sodium iodide (10 g, 66.7 mmoles) in dry dimethylformamide (300 ml) at 130° for 25 h. The cooled mixture was diluted with water and extracted with ether. The extracts were washed, dried, and fractionated to give the pure acetate (6.22 g, 70%).

The following were prepared in essentially the same way (yields in brackets): *2-fluoroethyl acetate* (52%), *2-fluoropropyl acetate* (79%), *2-fluorobutyl acetate* (85%), *2-fluoroheptyl acetate* (78%), *2-fluorooctyl acetate* (71%), and *2-fluorodecyl acetate* (73%). Also prepared by the same method was *methyl 11-acetoxy-10-fluoroundecanoate* (74%) starting from methyl 11-bromo-10-fluoroundecanoate.

2-Fluorohexyl Azide

1-Bromo-2-fluorohexane (14.3 g, 78.2 mmoles) and sodium azide (7.1 g, 109 mmoles) were stirred and heated under reflux in 87% aqueous dimethylformamide (160 ml) for 23 h at 130°. Isolation by ether extraction and purification in the usual way gave the azide (9.52 g, 84%).

2-Fluorohexyl Iodide

1-Bromo-2-fluorohexane (10 g, 54.6 mmoles), sodium iodide (9.5 g, 63.2 mmoles), and acetone (50 ml) were heated under reflux for 22 h. Isolation and purification in the usual manner gave the iodide (10.8 g, 86%). Redistillation from mercury gave a stable liquid, which remained colorless on storing over clean, dry copper turnings in a brown bottle.

2-Fluorodecyl iodide was prepared by the same procedure in 72% yield.

2-Fluorohexyl Formate

1-Bromo-2-fluorohexane (10 g, 54.6 mmoles) was stirred with a suspension of dry sodium formate (6.8 g, 100 mmoles) and sodium iodide (9.0 g, 60 mmoles) in dimethylformamide (300 ml). The mixture, protected from atmospheric moisture, was heated under reflux at 103–105° for 48 h. Isolation and purification in the usual way gave the formate (5.4 g, 67%).

2-Fluoroheptyl formate was prepared in the same way in 77% yield.

Hydrolysis of 2-Fluoroheptyl Formate

2-Fluoroheptyl formate (7.76 g, 52.4 mmoles), 6 *N* hydrochloric acid (35 ml), and dioxane (40 ml) were stirred magnetically at room temperature. The mixture became homogeneous after 40 min, and g.l.c. analysis indicated that only 8% of the formate remained after 4 h. The stirring was continued for 6 h more, and the product was isolated in the usual way. The yield of 2-fluoro-1-heptanol was 5.66 g (81%). The hydrogen n.m.r. spectrum (30.7 w/v % in CCl_4) showed peaks at 0.91 and 1.35 p.p.m. due to the terminal methyl and to the methylene groups respectively; the OH appeared at 3.98 p.p.m. The CH_2OH appeared as a doublet of doublets centered at 3.57 p.p.m. with J_{HF} 24.1, J_{HH} 4.8 c.p.s. The CHF group appeared as a pair of multiplets centered at 4.43 p.p.m. (J_{HF} 51.6 c.p.s.).

2-Fluorohexyl Nitrate

1-Bromo-2-fluorohexane (10 g, 54.6 mmoles) and silver nitrate (12.3 g, 72.4 mmoles) were dissolved in acetonitrile (50 ml), and the solution was heated under reflux at 120° for 27 h. (After 5 h, only 72% of the theoretical amount of silver bromide had been formed.) Isolation and purification gave the pure nitrate (7.54 g, 84%).

2-Fluoro-2-phenylethyl nitrate was prepared in 76% yield from 1-bromo-2-fluoro-2-phenylethane by the same procedure; the first sample for analysis decomposed before reaching its destination, emphasizing its instability.

2-Fluorohexyl Thiocyanate

1-Bromo-2-fluorohexane (7.0 g, 38.2 mmoles), potassium thiocyanate (7.0 g, 72.0 mmoles), and 95% ethanol (25 ml) were heated under reflux at 110° for 20 h. Isolation and purification in the usual way gave

the thiocyanate (4.42 g, 72%). This compound is moderately toxic to mice by intraperitoneal injection; LD_{50} 26.63 (19.43–36.57) mg/kg.

2-Fluorooctadecyl p-Nitrobenzoate

Lithium *p*-nitrobenzoate was prepared from a suspension of the acid in methanol by neutralization with aqueous lithium hydroxide. Concentration to small bulk and addition of ether induced the salt to crystallize. Yield: 98%. Crude 1-bromo-2-fluorooctadecane (see above) (15.68 g, 44.7 mmoles), dry lithium *p*-nitrobenzoate (13.4 g, 77.4 mmoles), sodium iodide (8.0 g, 53.4 mmoles), and dimethylformamide (500 ml) were mixed, and *p*-nitrobenzoyl chloride (27.8 g, 149.5 mmoles) was added as a scavenger for water. The solution was refluxed with stirring at 115° for 40 h. A further 7.5 g (43.3 mmoles) of lithium *p*-nitrobenzoate was added, and the heating was continued for a further 31 h. Isolation by ether extraction, washing and drying of the extract, and removal of the solvent gave an oil which crystallized on desiccation at 0.5 mm over P_2O_5. Slow crystallization from ethanol–ligroin (35–60°) followed by recrystallization from 95% ethanol gave 10.6 g (55%) of the ester.

2-Fluorooctadecyl p-Aminobenzoate

2-Fluorooctadecyl *p*-nitrobenzoate (4.6 g, 10.5 mmoles) dissolved in 95% ethanol (100 ml) was hydrogenated at atmospheric pressure using platinum dioxide (200 mg). The theoretical hydrogen uptake was complete after about 5 h. The hydrogenation flask was purged with nitrogen, and conc. hydrochloric acid (20 ml) was added. The catalyst was removed by filtration and water (80 ml) was then added to the filtrate. Yield: 4.02 g (86%) of the hydrochloride salt. The hydrochloride salt was recrystallized three times from ethanol and was then heated at 61° for 4 h at 0.2 mm over P_2O_5 in an Abderhalden pistol, thus giving the free *p*-aminobenzoate (Cl^- negative). The infrared spectrum ($CHCl_3$) showed NH stretch at 3 370 cm^{-1} (w), C=O stretch at 1 711 cm^{-1} (s), and C=C (aromatic) at 1 622 and 1 607 cm^{-1}.

1,3-Bistosyloxy-2-fluoropropane

A mixture of 1,2-dibromo-3-fluoropropane and 1,3-dibromo-2-fluoropropane as prepared above (2.0 g, 9.1 mmoles) and silver *p*-toluenesulfonate (5.0 g, 17.9 mmoles) in acetonitrile (15 ml) was heated under reflux for 112 h, by which time 62% of the theoretical quantity of silver bromide had been formed. The silver salts were removed by filtration and were washed with acetonitrile. Ether was added to the mixture, followed by distilled water to dissolve the unchanged silver tosylate. The ether layer was separated, washed, and dried (Na_2SO_4). Removal of the ether and the acetonitrile at 100 mm gave a syrupy residue, which, on standing overnight in the refrigerator, gave 150 mg of crystals, m.p. 95–105°. Addition of ether to the viscous filtrate gave a further 480 mg, m.p. 108–110°. Total yield: 45%. Recrystallization twice from 95% ethanol gave fine, colorless needles, m.p. 111–112°. An authentic sample, prepared by tosylation of 2-deoxy-2-fluoroglycerol (19) and kindly provided by Dr. P. W. Kent, had m.p. 107–110°, mixed m.p. 108–111°. The toxicity of this fluorotosylate, by intraperitoneal injection into mice, was > 100 mg/kg.

1,2-Dicyanohexane

In an attempt to prepare 3-fluoroheptanonitrile, dried sodium cyanide (3.4 g, 69.5 mmoles) in dry dimethyl sulfoxide (30 ml) was warmed to 88°. 2-Fluorohexyl bromide (10.0 g, 54.7 mmoles) was then added dropwise to this suspension (10 min). The mixture was heated at 90° for a further 40 min. The thick, cooled mixture was diluted with ether (100 ml) and then washed with water. The washings were extracted with ether, and the combined ether extracts were dried (Na_2SO_4). Removal of the ether and distillation of the residue gave 2.63 g (56%) of 1,2-dicyanohexane.

C. Hydrogenations

Attempted Hydrogenolysis of 1-Iodo-2-fluorohexane, 1-Iodo-2-fluorodecane, and trans-1-Bromo-2-fluorocyclohexane

No hydrogenolysis occurred at atmospheric pressure using hydrogen and platinum dioxide in various solvents (methanol, ethanol, and glacial acetic acid). Even ultraviolet irradiation with a Hanovia low-pressure mercury lamp did not appear to promote hydrogenolysis. Under the same conditions (no irradiation), 1,2-dibromocyclohexane readily formed cyclohexane.

Hydrogenolysis of a Mixture of 1,2-Dibromo-3-fluoropropane (III) and 1,3-Dibromo-2-fluoropropane (II)

An approximately equal mixture of the above compounds (6.25 g, 28.4 mmoles) in 95% ethanol (30 ml) was hydrogenated at room temperature and atmospheric pressure, using platinum dioxide (300 mg) as catalyst. Hydrogen (720 ml) was absorbed over a 25 h period. Gas–liquid chromatography showed that the mixture now contained only 11% of III. Removal of the catalyst, isolation of the product, drying (Na_2SO_4), and purification by fractionation gave initially a mixture of the isomeric dibromofluoropropanes, followed by pure II. The latter was at least 98% pure by g.l.c. analysis.

Hydrogenolysis of 1-Bromo-2-fluoro-2-phenylethane

The fluorobromide (10.24 g, 50.5 mmoles) in 95% ethanol (40 ml) was hydrogenated as above, using platinum dioxide (150 mg). Hydrogen uptake (2 440 ml) was complete in about 10 h. Removal of the catalyst, isolation, drying, and purification by fractionation gave a mixture (4.02 g) consisting of 87 mole % of ethylbenzene and 13 mole % of ethylcyclohexane (g.l.c. at 155° on an Apiezon-L column). These two products were identified by comparison of their retention times with authentic samples.

Hydrogenolysis of 2-Fluorohexyl Nitrate

2-Fluorohexyl nitrate (5.05 g, 30.6 mmoles) was hydrogenated at atmospheric pressure using platinum dioxide (60 mg) in ethanol (50 ml) containing acetic acid (1.8 g, 30 mmoles). Hydrogen absorption began at once and was steady at about 10 ml/min. When about 90% had been taken up, absorption ceased. The catalyst was removed by filtration and was washed with methanol. The filtrate was diluted with ether (250 ml) and the solution was washed with water, with brine, and again with water. Drying (Na_2SO_4), removal of the ether, and distillation gave 2-fluoro-1-hexanol (2.47 g, 67%), identical in all respects with the material obtained by the hydrolysis of 1-bromo-2-fluorohexane (see above).

Hydrogenolysis of 2-Fluoro-2-phenylethyl Nitrate

The nitrate (1.12 g, 6.03 mmoles) was dissolved in 95% ethanol (20 ml) containing 6 *N* hydrochloric acid (2 ml). Platinum dioxide (65 mg) was added and the mixture was hydrogenated at room temperature and atmospheric pressure. After 7 h, 510 ml of hydrogen had been absorbed. The catalyst was removed by filtration, ether (100 ml) was added to the filtrate, and the ethereal solution was washed and dried (Na_2SO_4). Removal of the solvent gave a liquid which, by infrared spectroscopy, was shown to be 2-phenylethanol. Further confirmation of the identity of the product was obtained by gas chromatography on two different columns (Apiezon-L and DEGS), and comparison of the retention times with those of an authentic sample.

ACKNOWLEDGMENTS

We wish to express our indebtedness to the National Research Council for financial support, and to Canadian Industries Limited, Montreal, for the award of a Fellowship (F. H. D.). We wish to acknowledge with thanks the gift of a sample of 1,3-bistosyloxy-2-fluoropropane from Dr. P. W. Kent, Department of Biochemistry, University of Oxford, England. We are grateful to Dr. M. K. McPhail and Dr. C. A. deCandole, Suffield Experimental Station, Ralston, Alberta for determining the toxicities, Dr. J. Newton for preparing 1-bromo-2-fluoro-1,2-diphenylethane, and Dr. J. B. Stothers of this department for help with the nuclear magnetic resonance spectra.

REFERENCES

1. R. L. Buchanan, F. H. Dean, and F. L. M. Pattison. Preprints, Second International Symposium on Fluorine Chemistry, Estes Park, Colorado. 1962. p. 385.
2. A. Bowers. J. Am. Chem. Soc. **81**, 4107 (1959).
3. A. Bowers, L. C. Ibáñez, E. Denot, and R. Becerra. J. Am. Chem. Soc. **82**, 4001 (1960).
4. A. Bowers, E. Denot, and R. Becerra. J. Am. Chem. Soc. **82**, 4007 (1960).
5. F. L. M. Pattison, R. L. Buchanan, and F. H. Dean. Can. J. Chem. This issue.
6. G. Schrader. British Intelligence Objectives Subcommittee, Report No. 1808.
7. R. E. Buckles and D. F. Knaack. J. Chem. Ed. **37**, 298 (1960).
8. P. B. D. de la Mare and J. G. Pritchard. J. Chem. Soc. 3910 (1954).
9. P. B. D. de la Mare, P. G. Naylor, and D. L. H. Williams. J. Chem. Soc. 443 (1962).
10. P. B. D. de la Mare, P. G. Naylor, and D. L. H. Williams. J. Chem. Soc. 3429 (1963).
11. J. Hine and W. H. Brader, Jr. J. Am. Chem. Soc. **75**, 3964 (1953).
12. J. Hine. Physical organic chemistry. 2nd ed. McGraw-Hill Book Co., Inc., New York, N.Y. 1962. pp. 157–185.
13. P. Mirosevic-Sorgo and B. C. Saunders. Tetrahedron, **5**, 38 (1959).
14. J. F. King and R. G. Pews. Can. J. Chem. **42**, 1294 (1964).
15. I. L. Knunyants, O. V. Kil'disheva, and I. P. Petrov. J. Gen. Chem. USSR Eng. Transl. **19**, 87 (1949). I. L. Knunyants, O. V. Kil'disheva, and E. Bykhovskaya. J. Gen. Chem. USSR Eng. Transl. **19**, 93 (1949).
16. J. Hine. Physical organic chemistry. 1st ed. McGraw-Hill Book Co., Inc., New York, N.Y. 1956. pp. 266–282.
17. J. Bornstein and M. R. Borden. Chem. Ind. London, 441 (1958).
18. F. W. Hoffmann. J. Org. Chem. **14**, 105 (1949).
19. N. F. Taylor and P. W. Kent. J. Chem. Soc. 2150 (1956).
20. F. L. M. Pattison and W. C. Howell. J. Org. Chem. **21**, 748 (1956).
21. J. E. Millington and F. L. M. Pattison. Can. J. Chem. **34**, 1532 (1956).