TOXIC FLUORINE COMPOUNDS

XIII. ω-FLUOROALKYL ETHERS[1,2]

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ABSTRACT

Representative ω-fluoroalkyl ethers have been synthesized. Their toxicological properties provide evidence for the rupture *in vivo* of the ether link. The compound 2-fluoro-1′,2′,2′,2′-tetrachlorodiethyl ether (XIII) shows outstanding activity as a systemic insecticide.

The characteristic toxicological properties of the ω-fluorine atom have been outlined in earlier reports in this series. In this paper are described representative ω-fluoroalkyl ethers (Table I), prepared for comparison with the ω-fluoroalcohols (16). It was maintained that if the toxicities of these ethers followed the usual dichotomous pattern (16), one could argue that the ether link was being split *in vivo*, giving the corresponding ω-fluoroalcohols.

PREPARATION

First to be examined were two ω-fluoroalkyl methyl ethers, $F(CH_2)_nOCH_3$. 6-Fluorohexyl methyl ether was prepared initially by treatment of 6-fluorohexyl bromide with sodium methylate (23% yield); however, considerable quantities of 6-fluoro-1-hexene were also isolated, indicating that milder conditions were necessary. Consequently the method of Stevens and Deans (20) was examined and found to be satisfactory. This involves the addition of the appropriate alcohol to sodium naphthalene (19) and treatment of the resultant alkoxide with methyl iodide. 5-Fluoroamyl and 6-fluorohexyl methyl ethers were thus obtained in yields of 37% and 75% respectively. The yield of 5-fluoroamyl methyl ether was subsequently raised to 70% by reversing the order of addition; thus, by slow addition of the sodium naphthalene to 5-fluoropentanol, the alcohol was always in excess and side reactions were minimized.

Three 4-fluorobutyl ethers were prepared by the following reactions:

$$\underset{\text{I}}{Cl(CH_2)_4O(CH_2)_4Cl} \xrightarrow{2KF} \underset{\text{II}}{F(CH_2)_4O(CH_2)_4F}$$

$$\underset{\text{I}}{Cl(CH_2)_4O(CH_2)_4Cl} \xrightarrow{KF} \underset{\text{III}}{F(CH_2)_4O(CH_2)_4Cl} \xrightarrow{NaCN} \underset{\text{IV}}{F(CH_2)_4O(CH_2)_4CN}$$

4,4′-Dichlorodibutyl ether (I), prepared (1, 2) from tetrahydrofuran, was readily converted to 4,4′-difluorodibutyl ether (II) (39% yield) by heating for 10 hours with excess anhydrous potassium fluoride in diethylene glycol at 125°. The fluorochloro ether (III) was prepared in 41% yield by the technique of partial fluorination (6, 15), whereby the reaction is carried out at a slightly higher temperature (130–150°) under reduced pressure,

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with the product being continuously removed by distillation. The fluorocyano ether (IV) was obtained in excellent yield by treatment of III with sodium cyanide. Attempted methanolysis of this to 4-fluoro-4′-carbomethoxydibutyl ether, using methanol and anhydrous hydrogen chloride, resulted in the formation of 4-fluorobutanol (4, 16) in 70.4% yield. The ether linkage is thus susceptible to hydrolytic cleavage even under these mild conditions; this is consistent with the biochemical behavior described below.

Following the observation of Schrader (18) that certain fluorinated polyethers, notably V and VI, are good systemic insecticides, and bearing in mind the ether linkage in the structure of the efficient contact insecticide 2-thiocyano-2′-*n*-butoxydiethyl ether (VII), we prepared two 2-fluoroethyl ethers for screening as contact and systemic insecticides. The first of these, 2-fluoro-2′-*n*-butoxydiethyl ether (X), is structurally similar to the

$$\underset{\text{V}}{F(CH_2)_2OCH_2O(CH_2)_2F} \qquad \underset{\text{VI}}{F(CH_2)_2O(CH_2)_2OCH_2O(CH_2)_2O(CH_2)_2F}$$

$$\underset{\text{VII}}{NCS(CH_2)_2O(CH_2)_2OC_4H_9}$$

thiocyanate (VII); it was prepared from butyl carbitol (VIII) by conversion to the bromide (IX), followed by fluorination:

$$\underset{\text{VIII}}{HO(CH_2)_2O(CH_2)_2OC_4H_9} \xrightarrow{PBr_3} \underset{\text{IX}}{Br(CH_2)_2O(CH_2)_2OC_4H_9}$$

$$\xrightarrow{KF} \underset{\text{X}}{F(CH_2)_2O(CH_2)_2OC_4H_9}$$

The second, 2-fluoro-1′,2′,2′,2′-tetrachlorodiethyl ether (XIII), contains both the 2-fluoroethyl ether group, referred to above, and the trichloromethyl group, associated with the well-known insecticide DDT; it was readily prepared from 2-fluoroethanol (XI) and chloral by treatment of the intermediate hemiacetal (XII) with phosphorus pentachloride:

$$\underset{\text{XI}}{F(CH_2)_2OH} \xrightarrow{CCl_3CHO} \underset{\text{XII}}{F(CH_2)_2OCH(OH)CCl_3} \xrightarrow{PCl_5} \underset{\text{XIII}}{F(CH_2)_2OCHClCCl_3}$$

Several simple 2-fluoroethyl ethers were prepared in the course of other work. 2-Fluoroethyl methyl ether and 2-fluorodiethyl ether have been described previously (17). 2-Fluoro-2′-chlorodiethyl ether and 2,2′-difluorodiethyl ether were prepared in low yield by fluorination of 2,2′-dichlorodiethyl ether with potassium fluoride in a stainless-steel autoclave; both compounds have been prepared by other workers (7, 8).

PROPERTIES

The toxicities of 5-fluoroamyl and 6-fluorohexyl methyl ethers (Table I) approximate those of 5-fluoropentanol and 6-fluorohexanol (16), and thus afford a priori evidence for the rupture of the ether linkage *in vivo*. Consistent with this mechanism are the toxicities of 2-fluoroethyl methyl ether (LD_{50} 15 mg./kg.), 2-fluoro-2′-*n*-butoxydiethyl ether (X), and 2-fluoro-1′,2′,2′,2′-tetrachlorodiethyl ether (XIII), all of which are similar to that of 2-fluoroethanol (LD_{50} 10 mg./kg.) (16) on a molar basis.

TABLE I

ω-FLUOROALKYL ETHERS: PHYSICAL CONSTANTS, TOXICITIES, AND ANALYTICAL RESULTS

Compound	Formula	Boiling point, °C.	mm.	n_D^{25}	LD_{50} for mice (intraperitoneal), mg./kg.	Analytical results: C, % Calc.	C, % Found	H, % Calc.	H, % Found	Other, % Calc.	Other, % Found
5-Fluoroamyl methyl ether	$F(CH_2)_5OCH_3$	127–128	740	1.3879	90					F 15.83	F, 15.6
6-Fluorohexyl methyl ether	$F(CH_2)_6OCH_3$	150–151	740	1.3966	4.0					F, 14.18	F, 13.9
4,4′-Dichlorodibutyl ether[a] (I)	$Cl(CH_2)_4O(CH_2)_4Cl$	128–130	13	1.4565	>100						
4,4′-Difluorodibutyl ether (II)	$F(CH_2)_4O(CH_2)_4F$	73.5–74	10	1.3962	0.82	57.81	57.88	9.70	9.72		
4-Fluoro-4′-chlorodibutyl ether (III)	$F(CH_2)_4O(CH_2)_4Cl$	100.5–101	10	1.4280	1.32	52.60	52.62	8.83	8.77	Cl, 19.41	Cl, 19.20
4-Fluoro-4′-cyanodibutyl ether (IV)	$F(CH_2)_4O(CH_2)_4CN$	134.5–135	10	1.4228	1.5	62.41	62.51	9.31	9.35		
2-Fluoro-2′-*n*-butoxydiethyl ether (X)	$F(CH_2)_2O(CH_2)_2OBu$	75–76	14	1.4048	43	58.54	58.54	10.37	10.41		
2-Fluoro-1′,2′,2′,2′-tetrachlorodiethyl ether (XIII)	$F(CH_2)_2OCHClCCl_3$	94–95	10	1.4735	48	20.89	20.61	2.19	2.24	Cl, 61.69 F, 8.26	Cl, 61.60 F, 8.0

[a] *Alexander and Schniepp (1) report b.p. 84–86° at 0.5 mm. and* n_D^{25} *1.4567.*

This biochemical cleavage of the ether linkage is strikingly confirmed by the results obtained with the four butyl ethers (I–IV). The dichloro ether (I), containing no fluorine, is non-toxic. The toxicities of the fluorochloro and fluorocyano ethers (III and IV) are almost identical, and both are very similar to that of 4-fluorobutanol, on a molar basis and within the limits of biological variation. The difluoro ether (II) can theoretically give rise to twice the quantity of 4-fluorobutanol on hydrolytic fission, and, according to expectation, is approximately twice as toxic as the two monofluoro ethers. The intimate relationship of these compounds can clearly be seen by considering the LD_{50} figures in terms of mg. *of fluorine*/kg. (Table II).

TABLE II

COMPARISON OF TOXICITIES OF 4-FLUOROBUTYL ETHERS

	LD_{50} for mice (intraperitoneal)	
	Mg. of compound/kg.	Mg. of fluorine/kg.
4-Fluorobutanol	0.9	0.18
4-Fluoro-4′-chlorodibutyl ether	1.32	0.14
4-Fluoro-4′-cyanodibutyl ether	1.5	0.16
4,4′-Difluorodibutyl ether	0.82	0.18

While the metabolic scission of methyl and ethyl *aromatic* ethers has long been recognized (3, 9, 21), little is known regarding the fate of *aliphatic* ethers *in vivo*. All of the above toxicity results provide circumstantial evidence for the rupture of ω-fluoroalkyl ethers in the animal body. It is probably not unreasonable to extend these conclusions to unfluorinated analogues by inferring the existence of a biological mechanism capable of promoting the rupture of simple aliphatic ethers.

All of the fluoroethers listed in Table I with the exception of IV have been tested as insecticides (12, 13), in particular for systemic activity. No appreciable phytotoxicity was observed with any of the compounds at the concentrations examined (0.1% or less). Contact toxicity was low for most of the members, but the butoxy ether (X) showed positive activity. Fumigant activity varied widely with the different compounds, with the butoxy ether (X) and 6-fluorohexyl methyl ether showing fairly strong activity. Systemic action was strong with several of the members, and outstanding with 2-fluoro-1′,2′,2′,2′-tetrachlorodiethyl ether (XIII) (14).

On preliminary testing, XIII appears to be about 15 times more potent than Schradan as a systemic insecticide; moreover, its mammalian toxicity (*ca.* 48 mg./kg., intraperitoneally to mice) appears to be less than that of Schradan (18 mg./kg., orally to rats). To compare the systemic activity of the two compounds, English broad bean seedlings, heavily infested with aphids, were washed free from soil and placed in different concentrations of the test solutions; the approximate insect mortality was observed after 24 and 48 hours. Results are shown in Table III. It can be seen that the fluoro ether (XIII) is active at concentrations as low as 1.3 p.p.m.

During the testing of XIII, the insect mortality continued to increase for at least three days. This may have been due to a relatively slow rate of translocation, and/or to some necessary biochemical transformation resulting in the formation of a more active species. It is not unlikely that the latter is 2-fluoroethanol, a compound which we have

TABLE III

MORTALITY OF *Aphis fabae* ON BROAD BEAN SEEDLINGS

Concentration of insecticide, %	Insect mortality, %			
	Compound XIII		Schradan	
	24 hr.	48 hr.	24 hr.	48 hr.
Control	0	0	0	0
0.02	98		64	
0.002	85		25	
0.001	41	90	17	50
0.0005	42	90	14	30
0.00025	27	90	2	30
0.00013	23	75	0	0

shown to be an effective systemic insecticide in its own right.[3] In line with our studies on mammalian toxicity (16), 3-fluoropropanol was found to be inactive as a systemic insecticide.

In order to demonstrate that both the 2-fluoroethyl and chlorine-containing moieties of XIII are essential for high activity, the following compounds, containing one but not both of the moieties, were tested:

2-fluoroethyl methyl ether, $FCH_2CH_2OCH_3$,

2-fluoro-2′-*n*-butoxydiethyl ether, $FCH_2CH_2OCH_2CH_2OBu$,

1,2,2,2-tetrachlorodiethyl ether (11), $CH_3CH_2OCHClCCl_3$.

All three were found to be less active than XIII, a fact implying that for high activity both moieties of XIII must be present in the same molecule.

EXPERIMENTAL[4]

6-Fluorohexyl Methyl Ether

(*a*) *From 6-fluorohexyl bromide.*—Clean metallic sodium (1.27 g., 0.05 g-atom) was dissolved in absolute methanol (5 g.), and to the solution was added 6-fluorohexyl bromide (15) (9 g., 0.054 mole). The mixture was heated under reflux for 2 hours, cooled, diluted with water, and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate. After removal of the ether, fractionation of the product gave 6-fluorohexyl methyl ether (1.5 g., 23%).

(*b*) *From 6-fluorohexanol.*—Sodium naphthalene was prepared (19) in an atmosphere of dry nitrogen. Small lengths of sodium wire (1.95 g.) were added to a solution of pure, dry naphthalene (10.7 g.) in pure, anhydrous 1,2-dimethoxyethane (100 ml.). The mixture was stirred vigorously. After about 15 minutes, the color changed to a dull green which gradually darkened as more sodium dissolved. The temperature was maintained at 20–25° by intermittent cooling. The sodium had dissolved completely after about 2 hours. 6-Fluorohexanol (16) was added slowly, and with vigorous stirring, to this freshly prepared solution of sodium naphthalene until there was a sharp color change from deep green to pale yellowish green, indicating that an equivalent of alcohol had been added. In this experiment, 5.0 g. of 6-fluorohexanol caused the permanent color change. The mixture was cooled to 20° or less, and methyl iodide (8.0 g.) was slowly added. Stirring

[3]*It is surprising that Schrader, in referring to the high acivity of certain of its esters, ethers, and acetals, has stated (18) that 2-fluoroethanol itself shows no activity as an insecticide.*

[4]*Physical constants and analytical results are listed in Table I.*

was continued for 1 hour after the addition was complete. The mixture was diluted with water (150 ml.) and extracted with ether. The extracts, after being dried over anhydrous sodium sulphate, were distilled, yielding a small forerun of 1,2-dimethoxyethane and then 6-fluorohexyl methyl ether (4.2 g., 75%).

5-Fluoroamyl Methyl Ether

Sodium naphthalene was prepared as described above, using naphthalene (12 g.) in 1,2-dimethoxyethane, and sodium (2.1 g.). This freshly prepared solution was slowly added to 5-fluoropentanol (16) (5 g.) through a delivery tube under nitrogen pressure until a permanent deep green color persisted. Vigorous stirring and cooling were employed throughout the reaction. A further quantity of 5-fluoropentanol was added until a final medium-green end point was attained. A total of 6.5 g. of 5-fluoropentanol was used. With cooling and stirring, methyl iodide (12 g.) was slowly added. Stirring was continued for 1 hour after the addition was complete. Isolation and purification were carried out as described above, yielding 5-fluoroamyl methyl ether (5.2 g., 70%).

4,4′-Difluorodibutyl Ether (II)

A mixture of 4,4′-dichlorodibutyl ether (I) (1, 2) (85 g., 0.43 mole), anhydrous potassium fluoride (80 g., 1.38 moles), and anhydrous diethylene glycol (400 g.) was heated with vigorous stirring at 125° for 10 hours. The mixture was cooled, diluted with an equal volume of water, and extracted with ether. The extracts were washed with water and dried over anhydrous sodium sulphate. After removal of the ether, the residue on distillation yielded crude 4,4′-difluorodibutyl ether (31.6 g., 45%). Redistillation gave the pure ether (27.6 g., 39%).

4-Fluoro-4′-chlorodibutyl Ether (III)

A mixture of 4,4′-dichlorodibutyl ether (I) (1, 2) (88.0 g., 0.44 mole), anhydrous potassium fluoride (38.0 g., 0.66 mole), and anhydrous diethylene glycol (400 g.) was placed in a 1-liter three-necked flask, equipped with a stirrer, a thermometer, and a vacuum distillation take-off. The pressure of the system was reduced to 30 mm., and the mixture was heated to 132°, whereupon a liquid started slowly to distill (b.p. 120–125°). For the next $2\frac{1}{2}$ hours, the reaction temperature was adjusted to give a slow, even rate of distillation, ultimately reaching 155°. The distillate (consisting of two layers) was dissolved in ether, washed successively with water, 10% aqueous sodium carbonate, and water again, and dried over anhydrous magnesium sulphate. After removal of the ether, the residue on fractionation yielded 4,4′-difluorodibutyl ether (3.4 g., 5.3%), 4-fluoro-4′-chlorodibutyl ether (26.3 g., 33% conversion, 41% yield), and finally unchanged 4,4′-dichlorodibutyl ether (18.1 g.).

4-Fluoro-4′-cyanodibutyl Ether (IV)

A mixture of 4-fluoro-4′-chlorodibutyl ether (III) (19.5 g., 0.107 mole), sodium cyanide (10.0 g., 0.204 mole), sodium iodide (16.0 g., 0.107 mole), and 80% ethanol (20 ml.) was heated under reflux for 4 hours. The mixture was cooled, diluted with water, and extracted with ether. The extracts were washed with water and dried over anhydrous sodium sulphate. After removal of the ether, the residue on fractionation through a modified Podbielniak column yielded the cyanide (IV) (16.9 g., 91%).

On attempted methanolysis to the corresponding ester using methanol and anhydrous hydrogen chloride, the only product isolated was 4-fluorobutanol (70.4%), of boiling

point 54–56° at 10 mm. and n_D^{25} 1.3958; Gryszkiewicz-Trochimowski (4) reports b.p. 52–53° at 11 mm.

2-Fluoro-2′-n-butoxydiethyl Ether (X)

Butyl carbitol (VIII) (100 g., 0.62 mole) was slowly added to phosphorus tribromide (83.8 g., 0.31 mole) with external cooling. The mixture was slowly heated to ensure completion of the reaction; this was accompanied by a series of small explosions in the reaction vessel, possibly due to peroxide decomposition. The mixture was cooled and diluted with water. The organic layer was separated, washed, dried, and distilled, yielding the crude bromide (IX) (106 g., 76%), of boiling point 99–104° at 13 mm. This was used in the subsequent fluorination without further purification.

A mixture of the crude bromide (IX) (100 g., 0.445 mole), anhydrous potassium fluoride (65 g., 1.12 moles), and butyl carbitol (500 g.) was heated at 140–150° for 10 hours with vigorous stirring. The contents of the flask were then directly distilled under reduced pressure through a 30 cm. Vigreux column until the boiling point of butyl carbitol was reached. The distillate was dissolved in ether and dried over anhydrous sodium sulphate. After removal of the ether, fractionation of the residue gave the fluoro ether (X) (11.5 g., 18%) and unreacted bromide (12 g.).

2-Fluoro-1′,2′,2′,2′-tetrachlorodiethyl Ether[5] *(XIII)*

Chloral (105.5 g., 0.715 mole) and 2-fluoroethanol (XI) (5) (63.6 g., 0.99 mole) were slowly mixed, and allowed to cool to room temperature. Freshly distilled, anhydrous ether (120 ml.) was added, and this solution of the hemiacetal (XII) was added slowly and with shaking to phosphorus pentachloride (199.0 g., 0.93 mole) in anhydrous ether (105 ml.). The temperature of the mixture was maintained between 15° and 20° by means of an ice bath. After it was left for 30 minutes, the mixture was poured onto crushed ice and stirred vigorously until the evolution of hydrogen chloride ceased. The resultant mixture was transferred to a large beaker immersed in ice, and an ice-cold 35% aqueous solution of sodium hydroxide was slowly added with stirring until the mixture was just alkaline to litmus. The mixture was steam distilled, and the organic layer was separated, washed, and dried over anhydrous calcium chloride. After removal of the ether, fractionation yielded the pure ether (XIII) (88.3 g., 53.5%).

Preparation of Solutions for Testing as Systemic Insecticides[6]

The following typical procedure was used for compounds which are only slightly soluble in water. 2-Fluoro-1′,2′,2′,2′-tetrachlorodiethyl ether (0.1 ml.) was dissolved in acetone (100 ml.), and a drop of Atlas Detergent No. G8916P was added. One milliliter of this solution was suspended in 100 ml. of water, thus giving a concentration of 0.001%. Serial dilutions gave the lower concentrations listed in Table III.

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