

General Anesthetics. 3. Fluorinated Methyl Ethyl Ethers as Anesthetic Agents

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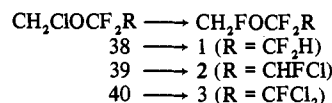
Thirty-four halogenated Me Et ethers have been synthesized and evaluated as volatile general anesthetics. Twelve had good anesthetic properties in mice and are suitable for study in larger species. Those fluorinated ethers having one H with at least 2 halogens other than F or 2 or more hydrogens with at least one Br or Cl were the best anesthetics.

We have previously reported the synthesis and anesthetic properties of some halogenated Me Et ethers.¹ Twenty of these ethers having mono-, di-, or trichloromethoxy groups have been treated with HF, SbF₃, or KF to yield mono- and difluoromethyl haloethyl ethers. Several of these compounds have good anesthetic properties in mice.

Synthesis. The fluorination of organic compounds by halogen exchange using antimony fluorides or HF is a well-known reaction.²⁻⁵ This method, discovered by Swarts in 1892, has been used mostly with hydrocarbons. Little work has been reported on the fluorination of aliphatic ethers. Booth and Burchfield⁶ in 1935 reported the fluorination of CH₂ClOCHCl₂ with SbF₃ to give CHF₂OCH₂Cl and CHF₂OCH₂F.^{7,8} Later work has been published on the fluorination of other bis(chloromethyl) ethers.⁸ The fluorination of CCl₃CHClOR (R = CH₃, C₂H₅, C₃H₇, and C₄H₉) was studied using a variety of fluorinating agents.⁹

Only the α-Cl was exchanged. Similarly, treatment of CCl₃CCl₂OCH₃ and CCl₃CCl₂OCCL₂CCl₃ with SbF₃ replaced only the α-Cl.¹⁰ We have recently reported the synthesis of some fluorinated Me *i*-Pr ethers using the Swarts reaction.¹¹ Alkali metal fluorides have also been used to replace halogens in aliphatic ethers.¹²⁻¹⁷

We have used both the Swarts reaction and alkali metal fluorides to prepare the 34 fluoromethyl haloethyl ethers listed in Table I. The conditions of these fluorinations with the appropriate chloromethyl starting materials are summarized in Table II. The monochloromethyl ethers 38, 39,



and 40¹ were fluorinated in low yield by both methods.

Table I

Compound	Bp (760 mm), °C	n _D ²⁰	Anal. ^c	Pharmacology
1, CH ₂ FOCF ₂ CF ₂ H	53		C, H	Anesthetic at 8%
2, CH ₂ FOCF ₂ CHFCl	83.5	1.3280	C, H, F	Anesthetic at 2.5% with tremors
3, CH ₂ FOCF ₂ CFCl ₂	91.5	1.3499	C, H	Good anesthetic at 2.5%
4, CHFClOCH ₂ CF ₃	56.5	1.3177	C, H, F	Too unstable to test
5, CHF ₂ OCH ₂ CF ₃ ^a	29	1.2653		Very weak anesthetic at 10%
6, CHF ₂ OCHClCF ₃ ^a	48.5	1.3002		Good anesthetic at 2.5%
7, CHFClOCF ₂ CHF ₂	55	1.3022	C, H	Good anesthetic at 2.5%
8, CHF ₂ OCF ₂ CHF ₂ ^a	28.5			Light anesthesia at 12.5%
9, CHFClOCF ₂ CHFCl	87.5	1.3458	C, H	Good anesthetic at 2.5%
10, CHF ₂ OCF ₂ CHFCl ^a	56.5	1.3030		Good anesthetic at 1.9%
11, CHFClOCF ₂ CHFBr	105	1.3730	C, H	Anesthetic at 1.25%, convulsive properties
12, CHF ₂ OCF ₂ CHFBr	73	1.3313	C, H, F	Good anesthetic at 1.9%
13, CHF ₂ OCF ₂ CHCl ₂	87.5	1.3484	C, H, F	Anesthetic at 1.25%
14, CHFClOCF ₂ CFCl ₂	95	1.3612	C, H, F	Anesthetic, convulsant at 2.5%
15, CHF ₂ OCF ₂ CFCl ₂ ^a	64	1.3235		Anesthetic at 2.5%, convulsant at 5%
16, CHFClOCF ₂ CCl ₃	135	1.4038	C, H, F	Anesthetic at 1.25%
17, CHF ₂ OCF ₂ CCl ₃	100	1.3686	C, H, F	Anesthetic, convulsant at 5%
18, CHF ₂ OCF ₂ CFCIBr ^a	83	1.3510		Deep anesthesia at 2.5%
19, CFCI ₂ OCH ₂ CF ₃	70	1.3385	C, H, F	Deep anesthesia at 5%, convulsions
20, CF ₂ ClOCH ₂ CF ₃ ^a	37			Convulsant at 5%
21, CFCI ₂ OCHClCF ₃	93	1.3611	C, H	Anesthetic at 2.5%, poor respiration
22, CF ₂ ClOCHClCF ₃ ^a	53	1.3142		Weak anesthetic at 5%
23, CFCI ₂ OCF ₂ CF ₂ H	67.5	1.3265	F	Anesthetic at 5%, twitching
24, CF ₂ ClOCF ₂ CF ₂ H	33		C, H, F	Light anesthesia at 15%
25, CFCI ₂ OCF ₂ CHFCl	100.5	1.3648	C, H, F	Anesthetic at 1.9%
26, CF ₂ ClOCF ₂ CHFCl	64.5	1.3200	C, H, F	Anesthetic with convulsions at 5%
27, CFCI ₂ OCF ₂ CHFBr	116	1.3900	C, H, F	Anesthetic at 2%, bad side effects
28, CF ₂ ClOCF ₂ CHFBr	81	1.3465	C, H, F	Deep anesthesia at 5%
29, CFCI ₂ OCF ₂ CF ₂ Cl	77	1.3392	C, F	Convulsions at 5%
30, CF ₂ ClOCF ₂ CF ₂ Cl	42		C, F	Convulsions at 17.5%, toxic
31, CFCI ₂ OCF ₂ CFCl ₂ ^a	113	1.3790		Convulsions at 1.25%
32, CF ₂ ClOCF ₂ CFCl ₂	77.5	1.3391		Convulsions at 10%, toxic
33, CFCI ₂ OCF ₂ CFCIBr	131	1.4022	C, F	Not anesthetic ^d
34, CF ₂ ClOCF ₂ CFCIBr	94	1.3631	C, F	Convulsions at 2.5%
35, CF ₃ CHClBr ^b	50.2	1.3700		Good anesthetic at 2.5%
36, CH ₃ OCF ₂ CHCl ₂ ^b	105	1.3861		Anesthetic at 1.5%
37, CF ₃ CH ₂ OCH=CH ₂ ^b	43.7	1.3192		Good anesthetic at 7.5%

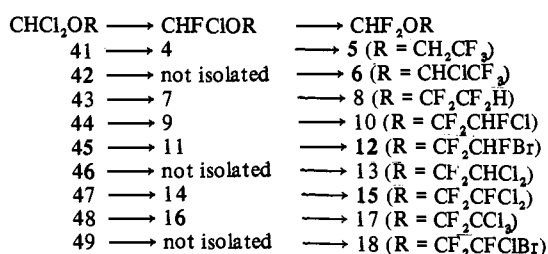
^aSynthesis of these compds by using different methods has been reported.¹ ^bReference standards. ^cMicroanalyses were done for the elements indicated and all results were within ±0.4% of the theoretical values. ^dTested in emulsion.

Table II. Fluorination of Chloro Ethers

Starting material	Method	Temp, °C	Wt % SbCl ₅	% yield	
				Monofluoro ether	Difluoro ether
38	B	0	2	10% 1	
	C	200		5-10% 1	
39	B	0	2	25% 2	
40	A	60	2	5% 3	
	C	200		5-10% 3	
41	B	-25	0	35% 4	
	B	0	0		35% 5
42	B	0	2.5		75% 6
43	B	0	5	80% 7	
	B	0	5		80% 8
44	A	70	1.5		70% 10
	B	0	2.5		88% 10
	B	-20	2	70% 9	3% 10
	B	50	0.25	72% 9	7% 10
45	A	60	1.5		35% 12
	B	0	5	50% 11	20% 12
46	A	75	2		40% 13
	B	0	2.5		55% 13
47	B	0	5	75% 14	
	B	0	5		75% 15
48	A	100	1		50% 17
	B	0	2.5	40% 16	
49	B	0	5		70% 18
50	B	0	0	75% 19	
	B	25	0	50% 19	35% 20
51	A	80	1	35% 21	15% 22
52	B	0	25	80% 23	
	B	0	5	40% 23	30% 24
53	A	60	2		45% 26
	B	0	5	80% 25	10% 26
54	B	0	5	15% 27	15% 28
55	B	0	20	80% 29	
	B	30	10	75% 29	5% 30
56	A	90	2		75% 32
	B	25	5	83% 31	4% 32
57	B	35	5	65% 33	15% 34

The KF method gave low yields resulting from thermal degradation at the required high reaction temp. The Swarts reaction gave low yields resulting from acidic cleavage of the CO bond.

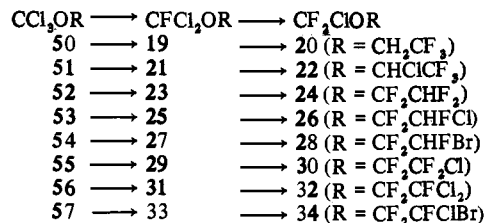
The dichloromethyl ethers 41-49 did not react with KF



but gave good yields of fluorination products in the Swarts reaction. The reaction could be done with ether SbF₃ or HF as the fluorinating agent and usually required a catalytic amount of pentavalent Sb. It was possible to replace only one Cl in good yield since the second Cl was less reactive. No halogens on the Et group were replaced in any of the reactions.

Fluorination of the Cl₃C group in the ethers 50-57 could also be done in good yield using the Swarts reaction to replace either 1 or 2 Cl atoms. The third Cl was not replaced in any of the reactions.

All the fluorination reactions clearly show a decrease in reactivity of the Cl on the MeO group with increasing F substitution. The Cl in CHCl₂O and CCl₃O is more reactive than in CHFClO and CFC₂O. The Cl in CF₂ClO is completely unreactive. Cl and Br in the Et group on C adjacent



to a CF₂ or CF₃ group are also completely unreactive. These results are not unexpected, since the Swarts reaction proceeds *via* an electron-deficient transition state.⁵ Hine has described the decreased reactivity of halogenated ethers and hydrocarbons in S_N1 reactions due to the inductive and mesomeric effects of halogen, especially F.¹⁸⁻¹⁹

Pharmacology. Substitution of F for Cl increased the stability and lowered the bp. All compounds were therefore suitable for testing as inhalation anesthetics except two; 4 was unstable and 33 had too high a boiling point.

Structure-activity relationships were in good general agreement with those previously reported.¹ It was again found that at least one H atom was necessary, since all the perhalogenated compounds (29-34) were weak anesthetics or convulsants.

The best anesthetics were those having 1 H with at least 2 halogens other than F or 2 or more H with at least one Cl or Br (2, 3, 6, 7, 9, 10, 12, 13, 16, 18, 25, and 28). Two of these, 6 and 10, are now in clinical trials.^{20,21}

Experimental Section

Pharmacology. All compds screened were at least 99.5% pure by glc. Pharmacology was done by J. C. Krantz, Jr., F. G. Rudo, and H. F. Cascorbi at the Department of Pharmacology, University of Maryland School of Medicine, Baltimore, Md., and The Huntingdon Research Center, Inc., Baltimore, Md., and A. B. Dobkin and P. H. Byles at the Department of Anesthesiology, State University of New York, Upstate Medical Center, Syracuse, N. Y., using the methods previously described.¹

Synthesis. Boiling points were detd by distn or by the Siwoloff method and are uncor. Synthesis of the 20 chloroethers (38-57) used for fluorination has been reported.¹

Fluorination of Chloro Ethers. The following 3 methods were used for fluorination and results of the fluorination reactions are given in Table II.

Fluorination Using SbF₃ (Method A). The chloro ether to be fluorinated was added slowly from a dropping funnel to a stirred mixt of SbF₃ (about 1 mole/mole of ether), and SbF₃ or SbCl₅ (about 2% by wt of the chloro ether). The reaction was started by adding a small amt of the chloro ether and heating to about 60° at which point the Sb salts turned dark and started to liquefy. The temp was then maintained at the bp of the product by adjusting the rate of addn of the ether or by external heating. The product was distd directly from the reaction mixt as formed or after the addn was complete. The crude ether, which contd some acid halides resulting from C-O bond cleavage, was washed with dil base, dried (K₂CO₃), and purified by distn or prep gas chromatog.

Fluorination with Anhydrous HF (Method B). Anhyd HF was added slowly *via* a calibrated plastic flowmeter to the chloro ether and SbCl₅ (0-20%, depending on the structure of the ether) contained in a 3-necked stainless steel flask fitted with a stirrer, thermometer well, and a copper Dry Ice condenser. The reaction was usually run at 0° with ice cooling or at room temp. The effluent HCl was led from the top of the Dry Ice condenser to a water scrubber. The amt of F exchange was estimated by titration of the scrubber, while controlling the rate of addn by use of the flowmeter. For partial fluorination the reaction was usually stopped when about 1 equiv of acid had been titrated and for complete fluorination when there was no more HCl evolved. The product was washed with H₂O, dried over K₂CO₃, and purified by distn or gas chromatog.

Fluorination with KF (Method C). KF (100 g) was added to *N*-methylpyrrolidone (500 ml) and the mixt dried by distg out 50 ml of the solvent. The chloro ether (100 g) was then added slowly with

stirring while keeping the reaction temp at 200° and distg a mixt of product and starting material from the reaction mixt. The distillate was washed with water, dried, and purified by fractional distn or preparative gas chromatog.

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General Anesthetics. 4. Methyl Pentahaloethyl and Methyl Heptahaloisopropyl Ethers as Anesthetic Agents

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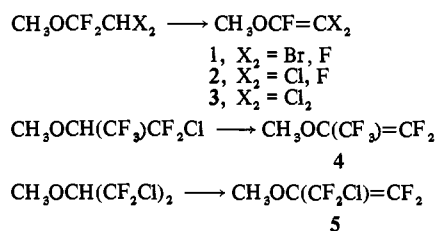
Twenty-two new perhaloethyl and perhaloisopropyl methyl ethers were synthesized. Nineteen were sufficiently stable to screen as general anesthetics. Both sedation and anesthesia were observed but the potency in general was diminished in comparison with a corresponding molecule with at least one H on the haloalkyl group.

Since the initial report of the anesthetic properties of fluorocarbons by Robbins¹ in 1946, many additional fluorocarbons and fluoro ethers have been evaluated as general anesthetics.^{2,3} Three of these are now in clinical use: fluroxene, CF₃CH₂OCH=CH₂; halothane, CF₃CHClBr; and methoxyflurane, CH₃OCF₂CHCl₂.

In the first papers of this series it was shown that many halogenated Me Et ethers^{4,5} and Me *i*-Pr ethers⁶ had general anesthetic activity although some were irritating and toxic. These compds all had at least one H on the Et or *i*-Pr group. We have continued these studies with a group of perhaloethyl and perhaloisopropyl ethers to determine the effect of the absence of the H atom and the increased halogen content. For this study, 12 methyl perhaloethyl ethers and 10 methyl perhaloisopropyl ethers were synthesized and evaluated for anesthetic activity, Table I.

Synthesis. All of the methyl pentahaloethyl ethers and methyl heptahaloisopropyl ethers were prepd by the same 3 steps: (a) synthesis of halogenated vinyl ethers followed by (b) addn of Cl or Br to the double bond and (c) exchange of the α-Br or -Cl for F using the Swarts reaction.

Vinyl ethers **1**, **2**, and **3** were synthesized by dehydrohal-

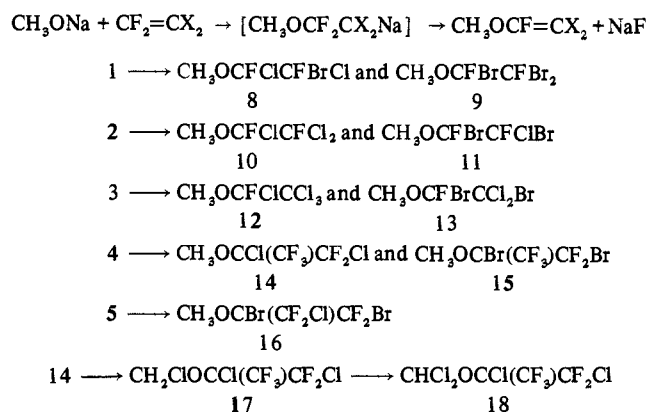


ogenation of satd ethers using KOH.^{7,8} The isopropenyl

ethers **4** and **5** were obtained using milder conditions, and the yields were better.

An alternate method for the prepn of the Me vinyl ethers, reaction of NaOMe with fluoroolefins in the absence of proton donors,⁹ was also used. The vinyl ethers were unstable to H₂O and air. They were halogenated without purification.

Both Cl and Br added readily to the double bond to give good yields of stable addition products. **14** was further chlorinated photochemically to give **17** and **18**.



When these ethers were heated with anhyd SbF₃ with a catalytic amount of SbCl₅, the Cl or Br adjacent to the O was replaced by F. No other halogens were replaced. Both **8** and **11** gave the same product **19**. Both **12** and CH₃OCCl₂CCl₃¹⁰ gave the same product **22**.

Fluorination of **14** replaced only the α-Cl to make **24**, identical with the product of CF₂Cl(CF₃)C=O, KF, and