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

Ross C. Terrell,* Louise Speers, Alex J. Szur, Thomas Ucciardi, and James F. Vitcha

*Central Research Laboratories, Airco, Inc., Murray Hill, New Jersey.* *Received December 6, 1971*

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, $SbF_3$, 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 Burchfield[6] in 1935 reported the fluorination of $CH_2ClOCHCl_2$ with $SbF_3$ to give $CHF_2OCH_2Cl$ and $CHF_2OCH_2F$.[7,8] Later work has been published on the fluorination of other bis(chloromethyl) ethers.[8] The fluorination of $CCl_3CHClOR$ (R = $CH_3$, $C_2H_5$, $C_3H_7$, and $C_4H_9$) was studied using a variety of fluorinating agents.[9] Only the α-Cl was exchanged. Similarly, treatment of $CCl_3CCl_2OCH_3$ and $CCl_3CCl_2OCCl_2CCl_3$ with $SbF_3$ 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**,

$$CH_2ClOCF_2R \longrightarrow CH_2FOCF_2R$$
$$38 \longrightarrow 1\ (R = CF_2H)$$
$$39 \longrightarrow 2\ (R = CHFCl)$$
$$40 \longrightarrow 3\ (R = CFCl_2)$$

and **40**[1] were fluorinated in low yield by both methods.

Table I

| Compound | Bp (760 mm), °C | $n^{20}D$ | *Anal.*[c] | Pharmacology |
|---|---|---|---|---|
| 1, $CH_2FOCF_2CF_2H$ | 53 | | C, H | Anesthetic at 8% |
| 2, $CH_2FOCF_2CHFCl$ | 83.5 | 1.3280 | C, H, F | Anesthetic at 2.5% with tremors |
| 3, $CH_2FOCF_2CFCl_2$ | 91.5 | 1.3499 | C, H | Good anesthetic at 2.5% |
| 4, $CHFClOCH_2CF_3$ | 56.5 | 1.3177 | C, H, F | Too unstable to test |
| 5, $CHF_2OCH_2CF_3$[a] | 29 | 1.2653 | | Very weak anesthetic at 10% |
| 6, $CHF_2OCHClCF_3$[a] | 48.5 | 1.3002 | | Good anesthetic at 2.5% |
| 7, $CHFClOCF_2CHF_2$ | 55 | 1.3022 | C, H | Good anesthetic at 2.5% |
| 8, $CHF_2OCF_2CHF_2$[a] | 28.5 | | | Light anesthesia at 12.5% |
| 9, $CHFClOCF_2CHFCl$ | 87.5 | 1.3458 | C, H | Good anesthetic at 2.5% |
| 10, $CHF_2OCF_2CHFCl$[a] | 56.5 | 1.3030 | | Good anesthetic at 1.9% |
| 11, $CHFClOCF_2CHFBr$ | 105 | 1.3730 | C, H | Anesthetic at 1.25%, convulsive properties |
| 12, $CHF_2OCF_2CHFBr$ | 73 | 1.3313 | C, H, F | Good anesthetic at 1.9% |
| 13, $CHF_2OCF_2CHCl_2$ | 87.5 | 1.3484 | C, H, F | Anesthetic at 1.25% |
| 14, $CHFClOCF_2CFCl_2$ | 95 | 1.3612 | C, H, F | Anesthetic, convulsant at 2.5% |
| 15, $CHF_2OCF_2CFCl_2$[a] | 64 | 1.3235 | | Anesthetic at 2.5%, convulsant at 5% |
| 16, $CHFClOCF_2CCl_3$ | 135 | 1.4038 | C, H, F | Anesthetic at 1.25% |
| 17, $CHF_2OCF_2CCl_3$ | 100 | 1.3686 | C, H, F | Anesthetic, convulsant at 5% |
| 18, $CHF_2OCF_2CFClBr$[a] | 83 | 1.3510 | | Deep anesthesia at 2.5% |
| 19, $CFCl_2OCH_2CF_3$ | 70 | 1.3385 | C, H, F | Deep anesthesia at 5%, convulsions |
| 20, $CF_2ClOCH_2CF_3$[a] | 37 | | | Convulsant at 5% |
| 21, $CFCl_2OCHClCF_3$ | 93 | 1.3611 | C, H | Anesthetic at 2.5%, poor respiration |
| 22, $CF_2ClOCHClCF_3$[a] | 53 | 1.3142 | | Weak anesthetic at 5% |
| 23, $CFCl_2OCF_2CF_2H$ | 67.5 | 1.3265 | F | Anesthetic at 5%, twitching |
| 24, $CF_2ClOCF_2CF_2H$ | 33 | | C, H, F | Light anesthesia at 15% |
| 25, $CFCl_2OCF_2CHFCl$ | 100.5 | 1.3648 | C, H, F | Anesthetic at 1.9% |
| 26, $CF_2ClOCF_2CHFCl$ | 64.5 | 1.3200 | C, H, F | Anesthetic with convulsions at 5% |
| 27, $CFCl_2OCF_2CHFBr$ | 116 | 1.3900 | C, H, F | Anesthetic at 2%, bad side effects |
| 28, $CF_2ClOCF_2CHFBr$ | 81 | 1.3465 | C, H, F | Deep anesthesia at 5% |
| 29, $CFCl_2OCF_2CF_2Cl$ | 77 | 1.3392 | C, F | Convulsions at 5% |
| 30, $CF_2ClOCF_2CF_2Cl$ | 42 | | C, F | Convulsions at 17.5%, toxic |
| 31, $CFCl_2OCF_2CFCl_2$[a] | 113 | 1.3790 | | Convulsions at 1.25% |
| 32, $CF_2ClOCF_2CFCl_2$ | 77.5 | 1.3391 | | Convulsions at 10%, toxic |
| 33, $CFCl_2OCF_2CFClBr$ | 131 | 1.4022 | C, F | Not anesthetic[d] |
| 34, $CF_2ClOCF_2CFClBr$ | 94 | 1.3631 | C, F | Convulsions at 2.5% |
| 35, $CF_3CHClBr$[b] | 50.2 | 1.3700 | | Good anesthetic at 2.5% |
| 36, $CH_3OCF_2CHCl_2$[b] | 105 | 1.3861 | | Anesthetic at 1.5% |
| 37, $CF_3CH_2OCH{=}CH_2$[b] | 43.7 | 1.3192 | | Good anesthetic at 7.5% |

[a] Synthesis of these compds by using different methods has been reported.[1] [b] Reference standards. [c] Microanalyses were done for the elements indicated and all results were within ±0.4% of the theoretical values. [d] Tested in emulsion.

Table II. Fluorination of Chloro Ethers

| Starting material | Method | Temp, °C | Wt % $SbCl_5$ | % yield: Monofluoro ether | % yield: 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

$CHCl_2OR \longrightarrow CHFClOR \longrightarrow CHF_2OR$

41 → 4 → 5 (R = $CH_2CF_3$)
42 → not isolated → 6 (R = $CHClCF_3$)
43 → 7 → 8 (R = $CF_2CF_2H$)
44 → 9 → 10 (R = $CF_2CHFCl$)
45 → 11 → **12** (R = $CF_2CHFBr$)
46 → not isolated → 13 (R = $CF_2CHCl_2$)
47 → 14 → **15** (R = $CF_2CFCl_2$)
48 → 16 → 17 (R = $CF_2CCl_3$)
49 → not isolated → 18 (R = $CF_2CFClBr$)

but gave good yields of fluorination products in the Swarts reaction. The reaction could be done with ether $SbF_3$ 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 $Cl_3C$ 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 $CHCl_2O$ and $CCl_3O$ is more reactive than in CHFClO and $CFCl_2O$. The Cl in $CF_2ClO$ is completely unreactive. Cl and Br in the Et group on C adjacent

$CCl_3OR \longrightarrow CFCl_2OR \longrightarrow CF_2ClOR$

50 → 19 → 20 (R = $CH_2CF_3$)
51 → 21 → 22 (R = $CHClCF_3$)
52 → 23 → 24 (R = $CF_2CHF_2$)
53 → 25 → 26 (R = $CF_2CHFCl$)
54 → 27 → 28 (R = $CF_2CHFBr$)
55 → 29 → 30 (R = $CF_2CF_2Cl$)
56 → 31 → 32 (R = $CF_2CFCl_2$)
57 → 33 → 34 (R = $CF_2CFClBr$)

to a $CF_2$ or $CF_3$ group are also completely unreactive. These results are not unexpected, since the Swarts reaction proceeds *via* an electron-deficent transition state.[5] Hine has described the decreased reactivity of halogenated ethers and hydrocarbons in SN1 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 Siwoloboff 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 $SbF_3$ (Method A).** The chloro ether to be fluorinated was added slowly from a dropping funnel to a stirred mixt of $SbF_3$ (about 1 mole/mole of ether), and $SbF_5$ or $SbCl_5$ (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 ($K_2CO_3$), 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 $SbCl_5$ (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 $H_2O$, dried over $K_2CO_3$, 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.

## References


(1) R. C. Terrell, L. Speers, A. J. Szur, J. Treadwell, and T. R. Ucciardi, *J. Med. Chem.*, 14, 517 (1971).
(2) A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1958.
(3) M. Hudlicky, "Chemistry of Organic Fluorine Compounds," The MacMillan Co., New York, N. Y., 1962.
(4) A. K. Barbour, L. J. Belf, and M. W. Buxton, *Advan. Fluorine Chem.*, 3, 181 (1963).
(5) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1969.
(6) H. S. Booth and P. E. Burchfield, *J. Amer. Chem. Soc.*, 57, 2070 (1935).
(7) I. B. Douglass and G. H. Warner, *ibid.*, 78, 6070 (1956).
(8) G. A. Sokol'skii and M. A. Dmitriev, *J. Gen. Chem. USSR*, 31, 256 (1961).
(9) C. T. Mason and C. C. Allain, *J. Amer. Chem. Soc.*, 78, 1682 (1956).
(10) C. B. Miller and C. Woolf, U. S. Patents 2,803,665 and 2,803,666 (1957).
(11) L. Speers, A. J. Szur, R. C. Terrell, J. Treadwell, and T. R. Ucciardi, *J. Med. Chem.*, 14, 593 (1971).
(12) F. L. M. Pattison, W. C. Howell, and R. C. Woolford, *Can. J. Chem.*, 35, 141 (1957).
(13) E. Gryszkiewicz - Trochimowski, A. Sporzynski, and J. Wnuk, *Recl. Trav. Chim. Pays-Bas*, 66, 413 (1947).
(14) F. L. M. Pattison and J. J. Norman, *J. Amer. Chem. Soc.*, 79, 2311 (1957).
(15) G. Olah and A. Pavlath, *Acta Chim. Acad. Sci. Hung.*, 3, 431 (1953).
(16) E. D. Bergmann and S. Cohen, *J. Chem. Soc.*, 2259 (1958).
(17) C. V. Tullock and D. P. Coffman, *J. Org. Chem.*, 25, 2016 (1960).
(18) J. Hine and R. J. Rosscup, *J. Amer. Chem. Soc.*, 82, 6115 (1960).
(19) J. Hine, *ibid.*, 85, 3239 (1963).
(20) A. B. Dobkin, P. H. Byles, S. Ghanooni, and D. A. Valbuena, *Can. Anaesth. Soc. J.*, 18, 264 (1971).
(21) A. B. Dobkin, *Anesth. Analg. (Cleveland)*, 48, 477 (1969).


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

Louise Speers, Alex J. Szur, and Ross C. Terrell*

*Central Research Laboratories, Airco, Inc., Murray Hill, New Jersey 07974.* *Received December 6, 1971*

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 Robbins[1] 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, $CF_3CH_2OCH{=}CH_2$; halothane, $CF_3CHClBr$; and methoxyflurane, $CH_3OCF_2CHCl_2$.

In the first papers of this series it was shown that many halogenated Me Et ethers[4,5] and Me *i*-Pr ethers[6] 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 dehydrohalogenation of satd ethers using KOH.[7,8] The isopropenyl ethers **4** and **5** were obtained using milder conditions, and the yields were better.

$$CH_3OCF_2CHX_2 \longrightarrow CH_3OCF{=}CX_2$$

1, $X_2$ = Br, F
2, $X_2$ = Cl, F
3, $X_2$ = $Cl_2$

$$CH_3OCH(CF_3)CF_2Cl \longrightarrow CH_3OC(CF_3){=}CF_2 \quad \mathbf{4}$$

$$CH_3OCH(CF_2Cl)_2 \longrightarrow CH_3OC(CF_2Cl){=}CF_2 \quad \mathbf{5}$$

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 $H_2O$ 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**.

$$CH_3ONa + CF_2{=}CX_2 \rightarrow [CH_3OCF_2CX_2Na] \rightarrow CH_3OCF{=}CX_2 + NaF$$

$$\mathbf{1} \longrightarrow CH_3OCFClCFBrCl \text{ (}\mathbf{8}\text{) and } CH_3OCFBrCFBr_2 \text{ (}\mathbf{9}\text{)}$$

$$\mathbf{2} \longrightarrow CH_3OCFClCFCl_2 \text{ (}\mathbf{10}\text{) and } CH_3OCFBrCFClBr \text{ (}\mathbf{11}\text{)}$$

$$\mathbf{3} \longrightarrow CH_3OCFClCCl_3 \text{ (}\mathbf{12}\text{) and } CH_3OCFBrCCl_2Br \text{ (}\mathbf{13}\text{)}$$

$$\mathbf{4} \longrightarrow CH_3OCCl(CF_3)CF_2Cl \text{ (}\mathbf{14}\text{) and } CH_3OCBr(CF_3)CF_2Br \text{ (}\mathbf{15}\text{)}$$

$$\mathbf{5} \longrightarrow CH_3OCBr(CF_2Cl)CF_2Br \quad \mathbf{16}$$

$$\mathbf{14} \longrightarrow CH_2ClOCCl(CF_3)CF_2Cl \text{ (}\mathbf{17}\text{)} \longrightarrow CHCl_2OCCl(CF_3)CF_2Cl \text{ (}\mathbf{18}\text{)}$$

When these ethers were heated with anhyd $SbF_3$ with a catalytic amount of $SbCl_5$, 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 $CH_3OCCl_2CCl_3$[10] gave the same product **22**.

Fluorination of **14** replaced only the α-Cl to make **24**, identical with the product of $CF_2Cl(CF_3)C{=}O$, KF, and