General Anesthetics. 1. Halogenated Methyl Ethyl Ethers as Anesthetic Agents

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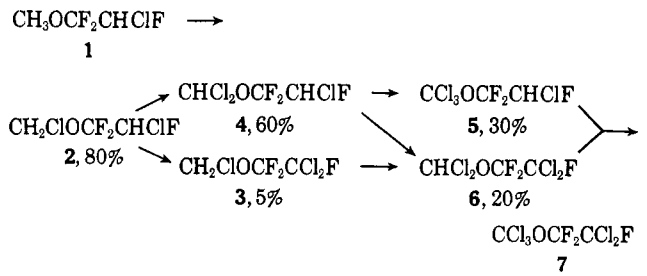
Thirty-six halogenated Me Et ethers have been synthesized for evaluation as volatile general anesthetics. Eleven of the ethers were too unstable to test, and, of the remaining 25, 13 had promising anesthetic properties in mice and are suitable for study in larger animals. Those ethers having one H with at least 2 halogens other than F or 2 or more H with at least one Br or one Cl were the best anesthetics.

The first study of the anesthetic properties of fluorinated hydrocarbons was reported by Robbins[1] in 1946. Since that time many fluorinated compounds, both hydrocarbons and ethers, have been found to have anesthetic properties in laboratory animals, and several have progressed to clinical trials in humans.[2,3] Three are presently in clinical use: fluroxene, $CF_3CH_2OCH{=}CH_2$; halothane, $CF_3CHClBr$; and methoxyflurane, $CH_3OCF_2CHCl_2$.

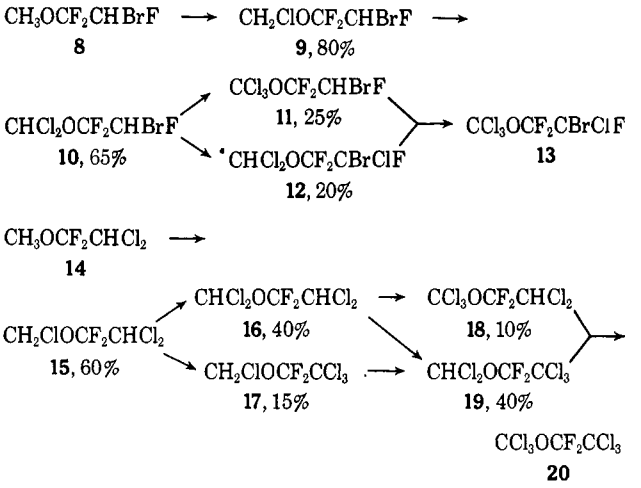
In an attempt to find a new agent superior to these three we have synthesized 36 new halogenated Me Et ethers by photochlorination and thermal bromination; 25 of these have been evaluated as anesthetics in mice (Table I). The remaining 11 were too unstable to test.

Synthesis.—All compounds were synthesized by photochlorination or thermal bromination of 9 fluorinated Me Et ethers. Chlorination of CH_3OCF_2CHClF (**1**) following the published procedure[4,5] gave mixtures of 6 chlorination products resulting from simultaneous chlorination of starting material and reaction products as outlined in the following equation. The percentage figures given represent the maximum percentages found in any chlorination mixture. The maximum amount of monochloro product was formed after reaction of about 1 mole of Cl_2, the maximum amounts of dichloro products after reaction of about 2 moles of Cl_2, and so forth. Yields of perhalogenated products were above 95%.

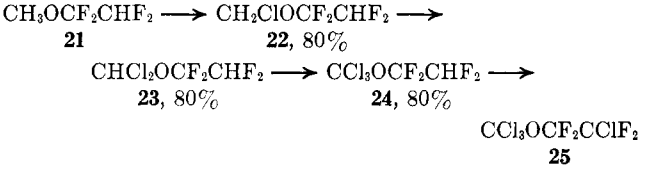


These results do not agree with those reported by Park[4,5] who described the reaction as "stepwise" and reported that the H on the CHClF carbon was the last to be replaced.

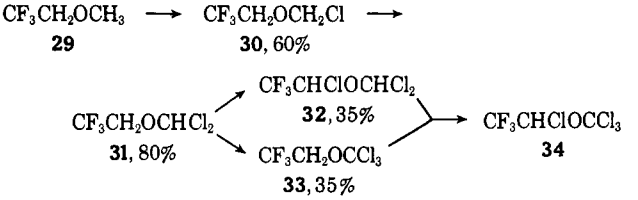
Similar results were found in the chlorination of both CH_3OCF_2CHBrF (**8**) and $CH_3OCF_2CHCl_2$ (**14**) except that the H of the OCF_2CHCl_2 group was more reactive and larger amounts of $CH_2ClOCF_2CCl_3$ (**17**) (corresponding to **3** were formed.



The reactivity of the CF_2CHCl_2 group compared to CF_2CHClF or CF_2CHBrF shows that chlorination is directed away from a C having an F substituent as well as away from a C adjacent to a F-substituted C as reported by Park.[4,5] This directive influence of F on the same C is also clearly shown in the chlorination of $CH_3OCF_2CHF_2$ (**21**) where the H on the CHF_2 group reacts very slowly and good conversions into the 3 products chlorinated on Me are found.



Additional examples of the directive influence of F substitution on the same C and on an adjacent C are found in the chlorination of $CF_3CH_2OCH_3$ (**29**) where CH_3O is more reactive than OCH_2CF_3 and good yields of $CHCl_2OCH_2CF_3$ (**31**) are formed and in the chlorination of $CF_3CH_2OHCF_2$ (**35**) where the $OCHF_2$ group is much less reactive than the CH_2 group adjacent to CF_3 and good yields of $CF_3CHClOCHF_2$ (**36**) and $CF_3CCl_2OCHF_2$ (**38**) are formed.

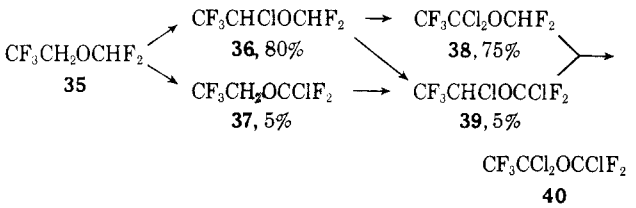


(1) B. H. Robbins, *J. Pharmacol. Exp. Ther.*, **86**, 197 (1946).
(2) J. C. Krantz, Jr., and F. G. Rudo, *in* "Handbook of Experimental Pharmacology," Vol. XX/1, O. Eichler, A. Farah, H. Herken, and A. D. Welch, Ed., Springer, Berlin, 1966, pp 501–564.
(3) E. R. Larsen, *Fluorine Chem. Rev.*, **3**, 1 (1969).
(4) J. D. Park, D. M. Griffin, and J. R. Lacher, *J. Amer. Chem. Soc.*, **74**, 2293 (1952).
(5) J. D. Park, B. Stricklin, and J. R. Lacher, *ibid.*, **76**, 1387 (1954).

TABLE I
PROPERTIES OF HALOGENATED METHYL ETHYL ETHERS

	Compd	Bp, °C (mm)	$n^{20}D$	Analyses[b]	Pharmacology
1	CH_3OCF_2CHClF[a]	70	1.3338		Light anesthesia at 2.5%
2	CH_2ClOCF_2CHClF[c]	110	1.3740		Too unstable to test
3	$CH_2ClOCF_2CCl_2F$	120	1.3885	C, H; nmr	Deep anesthesia at 1.5%
4	$CHCl_2OCF_2CHClF$[c]	118	1.3872		Too unstable to test
5	CCl_3OCF_2CHClF[c]	62 (50)	1.4089		Anesthetic and convulsant at 2.5%
6	$CHCl_2OCF_2CCl_2F$	53 (50)	1.3982	C, H, F; nmr	Toxic convulsant
7	$CCl_3OCF_2CCl_2F$[c]	69 (50)	1.4188		Convulsant at 0.6%
8	CH_3OCF_2CHBrF[d]	89	1.3662		Good anesthetic at 2.5%
9	CH_2ClOCF_2CHBrF	129	1.4035	C, H	Too unstable to test
10	$CHCl_2OCF_2CHBrF$	137	1.4130	C, H	Too unstable to test
11	CCl_3OCF_2CHBrF	62 (25)	1.4318	C, H, F; nmr	Anesthetic, toxic
12	$CHCl_2OCF_2CBrClF$	56 (25)	1.4229	C, H, F; nmr	Anesthetic, toxic
13	$CCl_3OCF_2CBrClF$	66 (20)	1.4410	C, F	Sedative, some ataxia
14	$CH_3OCF_2CHCl_2$[e]	105	1.3861		Anesthetic at 1.25%
15	$CH_2ClOCF_2CHCl_2$[c]	144	1.4187	C, H	Too unstable to test
16	$CHCl_2OCF_2CHCl_2$	154	1.4264	C, H	Too unstable to test
17	$CH_2ClOCF_2CCl_3$	157	1.4326	C, H; nmr	Too unstable to test
18	$CCl_3OCF_2CHCl_2$	172	1.4440	C, H; nmr	Too unstable to test
19	$CHCl_2OCF_2CCl_3$	166	1.4382	C, H; nmr	Too unstable to test
20	$CCl_3OCF_2CCl_3$	48 (5)	1.4551	C, F	Sedative, some ataxia
21	$CH_3OCF_2CHF_2$[f]	36.5	1.2939		Convulsant at 2.5%
22	$CH_2ClOCF_2CHF_2$[c]	77	1.3287	C, H	Too unstable to test
23	$CHCl_2OCF_2CHF_2$	85.5	1.3493	C, H	Deep anesthesia at 1.25%
24	$CCl_3OCF_2CHF_2$	105	1.3730	C, H, F; nmr	Good anesthetic at 5%
25	$CCl_3OCF_2CClF_2$	112	1.3815	C, F	Convulsant at 1.25%
26	$CH_3OCF_2CHBrCl$[g]	124	1.4183	C, H, F	Good anesthetic at 1.25%
27	$CHCl_2OCF_2CHBrCl$	173	1.4520	C, H, F; nmr	Too unstable to test
28	$CHCl_2OCF_2CBrCl_2$	186	1.4640	C, H, F; nmr	Too unstable to test
29	$CF_3CH_2OCH_3$[h]	31.2	1.2942		Weak anesthetic
30	$CF_3CH_2OCH_2Cl$	77	1.3340	C, H, Cl	Too unstable to test
31	$CF_3CH_2OCHCl_2$	91	1.3658	C, H, F	Anesthetic at 1.9%; irritating
32	$CF_3CHClOCHCl_2$	112	1.3882	C, H, F; nmr	Too unstable to test
33	$CF_3CH_2OCCl_3$	106	1.3861	C, H, F; nmr	Too unstable to test
34	$CF_3CHClOCCl_3$	63 (75)	1.4046	C, H; nmr	Toxic convulsant
35	$CF_3CH_2OCHF_2$	29	1.2653	C, H, F	Very weak anesthetic at 10%
36	$CF_3CHClOCHF_2$	48.5	1.3002	C, H, F	Good anesthetic at 2.5%
37	$CF_3CH_2OCClF_2$	37		C, H, F; nmr	Convulsant at 5%
38	$CF_3CCl_2OCHF_2$	60.5	1.3250	C, H, F	Anesthetic at 5%
39	$CF_3CHClOCClF_2$	53	1.3142	C, H, Cl	Weak anesthetic at 5%
40	$CF_3CCl_2OCClF_2$	74.5	1.3439	C, Cl	Convulsant at 5%
41	$CF_3CHBrOCHF_2$	64.5	1.3297	C, H	Good anesthetic at 1%
42	$CHF_2OCF_2CHF_2$	28.5		C, H	Light anesthesia at 12.5%
43	$CHF_2OCF_2CClF_2$	28		C, H; nmr	Not anesthetic at 5%
44	$CHF_2OCF_2CBrF_2$	45		C, H; nmr	Not anesthetic at 5%
45	CHF_2OCF_2CHClF[i]	56.5	1.3030	C, H	Good anesthetic at 1.9%
46	$CHF_2OCF_2CCl_2F$	64	1.3235	C, H, F	Anesthetic at 2.5%
47	$CHF_2OCF_2CBrClF$	83	1.3510	C, H, F; nmr	Deep anesthesia at 2.5%
48	$CHF_2CH_2OCHF_2$	55	1.2966	C, H	Very weak anesthetic at 5%
49	$CHF_2CHClOCHF_2$	74	1.3351	C, H, F	Anesthetic at 1.5%
50	$CF_3CHBrCl$[e]	50.2			Good anesthetic at 2.5%
51	$CF_3CH_2OCH{=}CH_2$[j]	43.7			Good anesthetic at 7.5%

[a] J. D. Park, D. K. Vail, K. R. Lea, and J. R. Lacher, *J. Amer. Chem. Soc.*, **70,** 1550 (1948). [b] Microanalyses were done for the elements indicated and all results were within ±0.4% of the theoretical values. Nmr spectra were recorded where indicated. All spectra were routine and were consistent with the assigned structures. [c] J. D. Park, D. M. Griffin, and J. R. Lacher, *J. Amer. Chem. Soc.*, **74,** 2293 (1952); J. D. Park, B. Stricklin, and J. R. Lacher, *ibid.*, **76,** 1387 (1954). [d] A. Demiel, *J. Org. Chem.*, **25,** 993 (1960). [e] Reference standard for comparison. [f] W. T. Miller, E. W. Fager, and P. H. Griswold, *J. Amer. Chem. Soc.*, **70,** 431 (1948). [g] A. Van Poznak and J. F. Artusio, Jr., *Toxicol. Appl. Pharmacol.*, **2,** 374 (1960). [h] A. L. Henne and M. A. Smook, *J. Amer. Chem. Soc.*, **72,** 4378 (1950). [i] R. C. Terrell, U. S. Patent 3,469,011 (to Air Reduction Co., Inc., New York, N. Y.), Sept 23, 1969 [*Chem. Abstr.*, **72,** 3025 (1970)].



The $OCHF_2$ group is also less reactive than OCF_2CHClF or OCF_2CHF_2 since chlorination of **42** and **45** gives good yields of the β-substitution products.

The thermal bromination of both **42** and **45** gives the corresponding bromo ethers **44** and **47**, but in lower yields, and the bromination of **35** gave **41** in low yield with many degradation products resulting from cleav-

$$CHF_2OCF_2CHF_2 \longrightarrow CHF_2OCF_2CClF_2$$
42 **43**, 80%

$$CHF_2OCF_2CHClF \longrightarrow CHF_2OCF_2CCl_2F$$
45 **46**, 80%

age of the C–O bonds. In none of the bromination reactions was any evidence of bromination of the CHF_2O group found.

$$CHF_2OCF_2CHF_2 \longrightarrow CHF_2OCF_2CBrF_2$$
42 **44** (25% conversion, 60% yield)

$$CHF_2OCF_2CHClF \longrightarrow CHF_2OCF_2CBrClF$$
45 **47** (60% conversion, 70% yield)

$$CF_3CH_2OCHF_2 \longrightarrow CF_3CHBrOCHF_2$$
35 **41** (15% yield)

Pharmacology.—All compounds which were stable were evaluated as anesthetic agents in mice. In general, those ethers having OCH_2Cl, $OCHCl_2$, or $OCCl_3$ groups were the least stable although some could be stabilized sufficiently to permit testing by the addition of K_2CO_3. Eleven new compounds (**9, 10, 16, 17, 18, 19, 27, 28, 30, 32,** and **33**) and 4 known compounds were too unstable to test (**2, 4, 15, 22**).

The anesthetic properties of 9 compounds (**1, 7, 8, 14, 26, 29, 35** plus $CF_3CHBrCl$ and $CF_3CH_2OCH{=}CH_2$ have been reported previously[1-3,6] and testing of these compounds was repeated for comparison with the new compounds. Our screening results were in good agreement with those reported.

About one-half of the compounds screened had good anesthetic activity in mice with the remainder about equally divided between very weak or inert compounds and convulsants.

In general, it was necessary to have at least one H present in order to have anesthetic activity as all the perhalogenated compounds (**7, 13, 20, 25, 40**) were weak anesthetics or convulsants. These results are in agreement with the observations of Krantz.[2]

Those compounds which had one H with at least 2 halogens other than F or 2 or more H with at least one Br or one Cl were the best anesthetics. Among these were 14 new compounds (**3, 11, 12, 23, 24, 39, 46, 31, 36, 38, 41, 45, 47, 49**), and all, except **31** which is irritating, are suitable for study in larger animals. Some of this work has been reported[6-8] and other studies are in progress.

(6) R. W. Virtue, L. O. Lund, McK. Phelps, Jr., J. H. K. Vogel, H. Beckivitt, and M. Heron, *Can. Anaesth. Soc. J.*, **13**, 233 (1966).

(7) A. B. Dobkin, R. G. Heinrich, J. S. Israel, A. A. Levy, J. F. Neville, Jr., and K. Ounkasen, *Anesthesiology*, **29**, 275 (1968).

(8) S. A. McDowell, K. D. Hall, and C. R. Stephen, *Brit. J. Anaesth.*, **40**, 511 (1968).

Experimental Section

Pharmacology.—All compds screened were routinely checked for purity by gas chromatography and all were 99.5% pure or better.

All screening was done using mice, and **6, 11, 12, 13, 20, 29,** and **34** were administered by ip injection as 0.6 *M* emulsions.[9] The remainder were administered by inhalation in admixture with O_2.[9] All 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.

Synthesis.—Boiling points were determined by distn or by the Siwoloboff method and are uncorr. Nmr spectra were detd in CCl_4 (Me_4Si) using a Varian A-60 spectrophotometer.

Compds **1, 8, 14, 21, 29, 42,** and **45** were prepared according to published procecures, referenced in Table I.

$CH_3OCF_2CHBrCl$ (26).—Na (75 g) was dissolved in abs MeOH (700 g), and $CF_3CHBrCl$[3] (540 g) was added slowly. After refluxing for 24 hr, the mixt was poured into H_2O (3 l.). The crude product (500 g) was fractionated to yield unreacted material (200 g), $CH_3OCF_2CHBrCl$ (125 g), bp 68° (100 mm), and $(CH_3O)_3CCHBrCl$ (125 g), bp 86° (10 mm), $n^{20}D$ 1.4727. *Anal.* ($C_5H_{10}BrClO_3$) C, H.

$CF_3CH_2OCHF_2$ (35) and $CHF_2OCH_2CHF_2$ (48).—Into the stainless steel liner of a 1-l. autoclave was placed a soln of 60 g (1 mole) of KOH pellets in 374 g (3.7 moles) of CF_3CH_2OH and 26 g (1.4 moles) of H_2O. The autoclave was then sealed and while being stirred and heated at 80–95°, 60 ml (0.8 mole) of liquefied $CHClF_2$ was added in increments to reach an autogenous pressure of 8.08 kg/cm². The autoclave was maintained at approx 90° for 2 hr after the addition of the reactants and was then cooled. The gases from the autoclave were vented through a Dry-Ice trap condensing 13 g of liq. The contents of the liner were distd to give 49 g of crude $CF_3CH_2OCHF_2$ (bp 27–40°) plus an additional 27 g collected in a Dry-Ice trap connected to the still. Low-temp distn of the combined 40 g from the Dry-Ice traps gave 24 g of recovered difluorochloromethane and 16 g more of $CF_3CH_2OCHF_2$. The combined product, 65 g, represents a 56.5% conversion of $CHClF_2$.

$CHF_2OCH_2CHF_2$ was synthesized from CHF_2CH_2OH in the same way with about 25% conversion.

Chlorination of Ethers.—All chlorinations were done by the method of Park.[4,5] The amount of Cl_2 was estimated by titration of the effluent HCl gas which was scrubbed into H_2O. Reaction mixts were analyzed using an F and M Model 202 chromatograph with thermistor detectors and a 3-m 10% nonylphenoxy(poly(ethylenoxy))ethanol, 15% Ucon LB-550-X on "Chromosorb" column, or a Wilkins aerograph Model A-350 with a hot wire detector and a 2-m Se 30 column. He flow was 50 cm³/min. Products were isolated by fractional distn, prep chromatography using a Wilkins "autoprep" chromatograph, or a combination of the two.

Bromination of Ethers.—Brominations were done by passing a stream of N_2 into a mixt of Br_2 and the ether and then through a 30 × 2.5 cm glass tube at 450–475°. Products were collected in a Dry-Ice trap and purified by distn or gas chromatography.

(9) H. F. Cascorbi and F. G. Rudo, *Anesth. Analg. (Cleveland)*, **43**, 163 (1964).