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 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**.

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

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

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

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

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

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

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

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

$(CH_3)_2SO_4$.[11] Compd **18** having three chlorines adjacent to the ether O gave only **27** where only the 2 Cl on the Me

$CH_3OCFClCFBrCl$ (**8**) ⟶ $CH_3OCF_2CFBrCl$ (**19**) ⟵ $CH_3OCFBrCFClBr$ (**11**)

$CH_3OCFBrCFBr_2$ (**9**) ⟶ $CH_3OCF_2CFBr_2$ (**20**)

$CH_3OCFClCFCl_2$ (**10**) ⟶ $CH_3OCF_2CFCl_2$ (**21**)

$CH_3OCFClCCl_3$ (**12**) ⟶ $CH_3OCF_2CCl_3$ (**22**) ⟵ $CH_3OCCl_2CCl_3$

$CH_3OCFBrCCl_2Br$ (**13**) ⟶ $CH_3OCF_2CCl_2Br$ (**23**)

14 ⟶ $CH_3OCF(CF_3)CF_2Cl$ (**24**)

$CH_3OCBr(CF_3)CF_2Br$ (**15**) ⟶ $CH_3OCF(CF_3)CF_2Br$ (**25**)

$CH_3OCBr(CF_2Cl)CF_2Br$ (**16**) ⟶ $CH_3OCF(CF_2Cl)CF_2Br$ (**26**)

$CHCl_2OCCl(CF_3)CF_2Cl$ (**18**) ⟶ $CHF_2OCCl(CF_3)CF_2Cl$ (**27**)

group were substituted. A similar structure to **27** was synthesized by direct chlorination. Of the 2 available H in $CHF_2OCH(CF_3)_2$[6] only the α-H on the *i*-Pr was replaced by Cl in low yield to make **28**.

$CHF_2OCH(CF_3)_2$ ⟶ $CHF_2OCCl(CF_3)_2$ (**28**)

Pharmacology. Of the 22 perhaloalkyl ethers synthesized (Table I) only 3 (**16**, **17**, and **18**) were acidic and too unstable to test. The remaining stable compounds were administered to mice either by inhalation of the vapor in O_2 or by ip injection of a 0.6 *M* emulsion of the liquid.[12] Fourteen compounds had some anesthetic activity, although most were toxic and 3 were only sedatives. Four Me Et ethers in the group, **8**, **12**, **19**, and **22**, gave satisfactory anesthesia in mice and study has been continued in larger animals.[13] The vinyl ether intermediates were generally too unstable to test. Only one, **4**, gave light anesthesia at 15%.

The major effect of the absence of the H atom and the increased halogen content is the alteration of the vapor pressure sufficiently to make many of the compounds unsuitable for inhalation administration. The replacement of H by Cl causes a rise in bp of about 20°, H by Br about 40°, while substitution by F lowers the bp around 20°. The compounds with lowered vapor pressure were administered by ip injection in a specially designed oil-in-water emulsion.[12] To make a comparison of the relative dosage by inhalation and ip injection, one anesthetic agent, methoxyflurane (**30**), was tested by both methods. The results are shown in Table II. Evaluation of the pharmacological results can be made on the basis of this standard.

The replacement of the sole H atom of a haloethyl or haloisopropyl group to make a perhaloalkyl group decreases the anesthetic potency with accompanying toxicity and unwanted side effects. These results are clear when **30** is compared with **21**, **22**, and **23** and when **29** is compared with **19** and **20**. The decrease in potency is more marked when the position of the H is adjacent to the O atom. In the isopropyl ethers compare **31** with **14**, **24**, and **27**. Substitution of F with Cl and Br enhances the potency as seen in **8** and **12**. These observations are an exception to the general rule

Table I

Compound	Bp (mm), °C	$n^{20}D$	*Anal.*	Pharmacology
1, $CH_3OCF{=}CFBr$	67	1.3933	C, H, Br	Too unstable to test
2, $CH_3OCF{=}CFCl$	57[a]	1.3611		Too unstable to test
3, $CH_3OCF{=}CCl_2$	101[b]	1.3942		Too unstable to test[c]
4, $CH_3OC(CF_3){=}CF_2$	32	1.2900	C, H, F	Light anesthesia at 15%, toxic
5, $CH_3OC(CF_2Cl){=}CF_2$	65.5	1.3424	C, H, Cl	Too unstable to test
6, $CH_3OCHClCCl_3$	49 (7)[g]	1.4840	C, H	Anesthetic in emulsion (0.15 ml), toxic
7, $CH_3OCCl{=}CCl_2$	47 (30)[d]	1.4800		Too unstable to test
8, $CH_3OCFClCFBrCl$	64.5 (51)	1.4395	C, H, F	Potent anesthetic by emulsion (0.1 ml)
9, $CH_3OCFBrCFBr_2$	49 (3.8)	1.5001	C, H, Br	Light anesthesia by emulsion (0.1 ml)
10, $CH_3OCFClCFCl_2$	66 (90)	1.4077	C, H, F	Anesthetic in emulsion (0.2 ml), toxic
11, $CH_3OCFBrCFClBr$	58 (15)[e]	1.4719	C, H, F	Anesthetic in emulsion (0.2 ml), toxic
12, $CH_3OCFClCCl_3$	57 (18)	1.4570	C, H, Cl	Anesthetic and analgetic in emulsion (0.1 ml)
13, $CH_3OCFBrCCl_2Br$	59 (3)		C, H, F	Sedative in emulsion (0.1 ml), toxic
14, $CH_3OCCl(CF_3)CF_2Cl$	96	1.3521	C, H, Cl	Anesthesia with irritation at 2.5%
15, $CH_3OCBr(CF_3)CF_2Br$	129	1.4050	C, H, Br	Anesthesia with excitation at 0.75%
16, $CH_3OCBr(CF_2Cl)CF_2Br$	65 (16)	1.4432	F	Not tested
17, $CH_2ClOCCl(CF_3)CF_2Cl$	125	1.3774	C, H, Cl	Too acidic to test
18, $CHCl_2OCCl(CF_3)CF_2Cl$	64 (54)	1.3874	Cl	Too unstable to test
19, $CH_3OCF_2CFBrCl$	102	1.3879	C, H, F	Potent anesthetic at 2.5% and in 0.3 *M* emulsion[i]
20, $CH_3OCF_2CFBr_2$	49 (45)	1.4197	C, H, F	Anesthetic, poor respiration, in emulsion (0.2 ml)
21, $CH_3OCF_2CFCl_2$[f]	83	1.3568	C, H, Cl	Anesthesia at 2.5%, poor respiration
22, $CH_3OCF_2CCl_3$	46 (46)[h]	1.4082	C, H, Cl	Good anesthetic at 1.5% and in emulsion (0.2 ml)
23, $CH_3OCF_2CCl_2Br$	59 (36)	1.4396	C, H, F	Sedative by emulsion (0.1 ml), toxic
24, $CH_3OCF(CF_3)CF_2Cl$	63	1.3053	C, H, Cl	No anesthesia at 7.5%
25, $CH_3OCF(CF_3)CF_2Br$	80	1.3303	C, H	Anesthesia with excitation at 5%
26, $CH_3OCF(CF_2Cl)CF_2Br$	114	1.3714	C, H, F	Anesthetic at 1.25%
27, $CHF_2OCCl(CF_3)CF_2Cl$	84	1.3247	C, H, Cl, nmr	Anesthesia with convulsions at 5%
28, $CHF_2OCCl(CF_3)_2$	45	<1.3	F	No anesthesia at 7.5%
29, CH_3OCF_2CHFBr	89[j]	1.3662		Good anesthetic at 2.5%
30, $CH_3OCF_2CHCl_2$[k]	105	1.3861		Anesthetic at 1.25% vapor and with 0.1-ml emulsion
31, $CH_3OCH(CF_3)CF_2Cl$	80[l]	1.3203		Anesthetic at 2.0%, irritant

[a] Reported bp 57.6°, $n^{25}D$ 1.3570 (ref 7). [b] Reported bp 54–54.5° (150), $n^{20}D$ 1.4260 (ref 8). [c] No anesthesia and toxic at <2% vapor concn (ref 3). [d] Reported bp 135–140° (ref 10). [e] Reported bp 68° (32), $n^{25}D$ 1.4696 (ref 7). [f] Prepd by BrF_3 addn to $CH_3OCF{=}CCl_2$.[17] [g] Reported bp 76–78° (23) (ref 10). [h] Reported bp 118–120° (ref 10). [i] See ref 18. Anesthetic activity attributed to **19** is actually for $CH_3OCF_2CHClBr$ (private communication, A. Van Poznak). [j] Ref 15. [k] Reference standard. [l] Ref 6.

Table II. Comparison of Inhalation and Injection[a]

Inhalation vapor, %	Ip injection, ml of 0.6 *M* emulsion	Average induction time, min	Average recovery time, min
1.25		1.38 ± 0.13	3.40 ± 2.2
2.50		0.71 ± 0.18	9.65 ± 4.18
	0.05 (11 induced)	2.25 ± 0.73	5.02 ± 3.16
	0.10 (17 induced)	1.66 ± 0.28	14.15 ± 7.40
	0.20 (17 induced)	1.40 ± 0.44	*b*

[a]Methoxyflurane (30) on 20 mice at each concn (ref 12). [b]14 deaths within first hour, 3 recovered after 1 hr.

that increased halogenation of ethers increases the potency,[2,3] and emphasizes the importance of the presence of an H atom and the absence of a perhaloalkyl group in a good anesthetic compound.

Experimental Section

Pharmacology. All compds were routinely checked for purity by glc and all compds evaluated as anesthetics were at least 99.5% pure. All screening was done using mice and **6**, **8**, **9**, **10**, **11**, **12**, **13**, **20**, and **23** were administered ip in a 0.6 *M* emulsion.[12] The remainder were administered by inhalation in admixt with O_2.[12] 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.

Synthesis. Boiling points were detd by distn or by the Siwoloboff method and are uncorrected. Where analyses are indicated only by symbols of the elements in Table I, analytical results obtained for these elements were within ±0.4% of the theoretical values.

The satd ethers used as starting materials for dehydrohalogenation were prepd according to published procedures.[14] The vinyl ethers **2**, **3**, and **5** were synthesized as illustrated for **1** and **4**. Vinyl ethers were halogenated by addn of the calcd amt of Cl or Br in the cold to give over 90% yield of the products **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, and **16**. All ethers were fluorinated using essentially the same method as illustrated for **20**.

Methyl 2-Bromo-1,2-difluorovinyl Ether (1). A soln of 23 g (1 g-atom) of Na in 200 ml of MeOH and 400 ml of xylene was distd to 100° to remove all the excess MeOH. The xylene slurry of NaOMe was placed in a 1-l. autoclave and mixed with 93 ml (1.05 moles) of CF_2=CFBr added through a pressurized buret. The mixt was stirred and heated at 100° (80 psi) for 20 hr. The cooled autoclave was vented and the contents were filtered. Fractionation of the liquid in a stream of N_2 gave 72 g of crude product, bp 72–80°. Refractionation under N_2 gave a small cut of 16 g, bp 67°. On standing in air the vinyl ether reacted exothermically releasing acidic vapors and a solid residue identified as oxalic acid.

Methyl 1,2-Dichloro-1,2-difluoro-2-bromoethyl Ether (8). A mixt of 400 g (2.07 moles) of CH_3OCF_2CHFBr[15] and 116 g of powd KOH was stirred and heated at reflux for 3 hr and then distd from the solid. The dist (approximately 30% vinyl ether in satd ether) was placed in a flask with a Dry Ice condenser and a gas inlet tube and treated with Cl_2 at such a rate to maintain the temp at −10 to 0°. The addn was contd until the yellow color of excess Cl_2 persisted. The crude product mixt was washed with dil Na_2CO_3 until neutral and dried (K_2CO_3). Vacuum distn sepd 171 g, bp 32–34° (80 mm), of satd ether CH_3OCF_2CHFBr and 68 g, bp 54–55° (34 mm), of crude dichloro ether. Prep chromatog isolated 8.9 g of a pure sample (99.9%) for anesthesia screening.

The two satd ethers, CH_3OCF_2CHFCl and $CH_3OCF_2CHCl_2$, were dehydrofluorinated by KOH with more vigorous exothermic results and required diluents such as aqueous Cellosolve or DMSO to temper the reaction. The conversions were low, 22–40%. The vinyl ethers in both cases were difficult to sep from the satd ethers and were chlorinated directly.

Methyl Perfluoroisopropenyl Ether (4). A soln of 78 g of KOH, 110 ml of H_2O, and 60 ml of Cellosolve in a 1-L flask was placed under a Vigreaux column. While stirring and heating at 70°, 203 g (1.02 moles) of methyl 1-chloro-1,1,3,3,3-pentafluoroisopropyl ether[16] was added at such a rate to maintain a steady take-off of crude vinyl ether at 30–40°. The 90-g distillate was washed with dil NaOH and redistd to give 80.5 g of **4**, bp 32°, 48% conversion.

Dichloromethyl 1,2-Dichloropentafluoroisopropyl Ether (18). Cl_2 was bubbled into 174 g (1.1 moles) of **4** cooled to 0° until 76 g (sufficient to react with the double bond) had been added. The temp was allowed to rise slowly to 80° while chlorination was contd under a 250-W lamp until 152 g of Cl_2 had been consumed (a total of 3.2 moles). The crude mixt was washed with aqueous K_2CO_3 and dried ($MgSO_4$). Vacuum distn yielded 4.5 g, bp 55–60° (56 mm), of crude $CH_2ClOCCl(CF_3)CF_2Cl$ and 259 g of $CHCl_2OCCl(CF_3)CF_2Cl$, bp 62–64° (54 mm).

Methyl 1,1,2-Trifluoro-2,2-dibromoethyl Ether (20). A mixt of 49.5 g (0.15 mole) of **9**, 26.6 g (0.15 mole) of SbF_3, and 5 drops of $SbCl_5$ was refluxed at 117° for 3 hr. The product was distd from the reaction mixt, washed with 1:1 HCl-H_2O, then with H_2O and dried ($MgSO_4$). Distn gave 26.2 g of $CH_3OCF_2CFBr_2$, bp 49° (15 mm).

Difluoromethyl 1,1,1,3,3-Pentafluoro-2,3-dichloroisopropyl Ether (27). A mixt of 124 g (0.41 mole) of **17**, 88.5 g (0.49 mole) of SbF_3, and 9.3 g of $SbCl_5$ was refluxed at 85° for 3 hr. The product was worked up as previously described. Distn gave 20 g of a crude forecut, bp 80–83°, and 80 g of **27**, bp 84°. The location of the two F atoms on the Me group was confirmed by the nmr spectrum of a $OCHF_2$ group. Pmr spectrum was detd in CCl_4 ($SiMe_4$) using a Varian A-60 spectrophotometer.

Difluoromethyl 1,1,1,3,3,3-Hexafluoro-2-chloroisopropyl Ether (28). $CHF_2OCH(CF_3)_2$[6] (80 g, 0.25 mole) was photochlorinated at 33–38° over a period of 7 hr. The uptake of Cl_2 was very slow. Based on HCl evolved, only 0.12 mole of Cl_2 reacted. Fractional distn gave 63 g of distillate at 42–44° contg approx 48% of a new compd. Prep chromatog isolated a pure sample of $CHF_2OCCl(CF_3)_2$, bp 45°, whose ir spectrum corresponded to the structure given.

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