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

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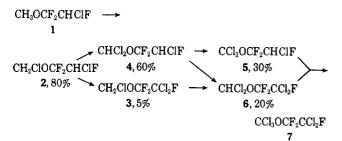
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Thirty-six halogenated Me Et ethers have been synthesized for evaluation as volatile general anesthetics. Eleven of the ethers were too unstable to test, and, of the remaining 25, 13 had promising anesthetic properties in mice and are suitable for 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 Robbins¹ 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

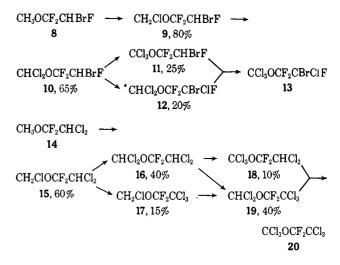
(1) B. H. Robbins, J. Pharmacol. Exp. Ther., 86, 197 (1946).

- (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).

and larger amounts of $CH_2ClOCF_2CCl_3$ (17) (corresponding to 3 were formed.



The reactivity of the CF₂CHCl₂ group compared to CF₂CHClF or CF₂CHBrF 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 CH₃OCF₂CHF₂ (**21**) where the H on the CHF₂ group reacts very slowly and good conversions into the 3 products chlorinated on Me are found.

$$\begin{array}{c} \mathrm{CH}_{3}\mathrm{OCF}_{2}\mathrm{CHF}_{2} \longrightarrow \mathrm{CH}_{2}\mathrm{CloCF}_{2}\mathrm{CHF}_{2} \longrightarrow \\ \mathbf{21} \qquad \mathbf{22}, \ 80\% \\ \mathrm{CHCl}_{2}\mathrm{OCF}_{2}\mathrm{CHF}_{2} \longrightarrow \mathrm{CCl}_{3}\mathrm{OCF}_{2}\mathrm{CHF}_{2} \longrightarrow \\ \mathbf{23}, \ 80\% \qquad \mathbf{24}, \ 80\% \\ \mathrm{CCl}_{3}\mathrm{OCF}_{2}\mathrm{CClF}_{2} \\ \mathbf{25} \end{array}$$

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 $CF_3CHCOCHF_2$ (36) and $CF_3-CCl_2OCHF_2$ (38) are formed.

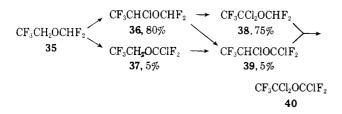
$$\begin{array}{cccc} \mathrm{CF_3CH_2OCH_3} & \longrightarrow & \mathrm{CF_3CH_2OCH_2Cl} & \longrightarrow \\ & & & & & \\ \mathbf{29} & & & & & \\ & & & & \\ \mathrm{CF_3CH_2OCHCl_2} & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & \\$$

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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						
$ \begin{array}{cccc} 4 & CHCloCF2CHCH^{+} & 118 & 1.3872 & Too metable to test \\ 5 & CCLoCF2CHCF^{+} & 62 (50) & 1.4982 & C, H, F; nmr \\ 6 & CHCloCF2CLF^{+} & 69 (50) & 1.4188 & Convulsant at 0.677 \\ 7 & CCLOCF2CHF^{+} & 89 & 1.3662 & Convulsant at 0.677 \\ 9 & CH2COCF2CHFF^{+} & 129 & 1.4052 & C, H \\ 10 & CHCloCF2CHFF^{+} & 127 & 1.4130 & C, H \\ 11 & CCLOCF2CHFF^{+} & 127 & 1.4130 & C, H \\ 12 & CHCloCF2CHFF^{+} & 56 (25) & 1.4229 & C, H, F; nmr \\ 13 & CCLOCF2CHFF^{+} & 56 (25) & 1.4229 & C, H, F; nmr \\ 14 & CH_2OCF2CHCF & 56 (25) & 1.4249 & C, H \\ 15 & CH2COCF2CHCF & 105 & 1.3861 & Too unstable to test \\ 16 & CHClOCF2CHCF & 105 & 1.3861 & Too unstable to test \\ 17 & CH2COCF2CHCF & 105 & 1.3861 & Too unstable to test \\ 18 & CCLOCF2CHCF & 166 & 1.4392 & C, H; nmr \\ 10 & CHCLOCF2CHCF & 166 & 1.4382 & C, H; nmr \\ 10 & CHCLOCF2CHCF & 166 & 1.4382 & C, H; nmr \\ 10 & CHCLOCF2CHCF & 166 & 1.4382 & C, H; nmr \\ 10 & CHCLOCF2CHCF & 166 & 1.4382 & C, H; nmr \\ 10 & CHCLOCF2CHCF & 166 & 1.4382 & C, H; nmr \\ 10 & UHCLOCF2CHCF & 166 & 1.4382 & C, H; nmr \\ 10 & UHCLOCF2CHCF & 30.5 & 1.2399 & Convulsant at 2.577 \\ 22 & CH2COCF2CHF & 165 & 1.3740 & C, H; nmr \\ 23 & CCLOCF2CHF & 165 & 1.3740 & C, H; nmr \\ 24 & CCLOCF2CHF & 165 & 1.3740 & C, H; nmr \\ 25 & CCLOCF2CHF & 165 & 1.3740 & C, H; nmr \\ 25 & CCLOCF2CHF & 165 & 1.3740 & C, H; nmr \\ 26 & CH2CF2CHF & 165 & 1.3740 & C, H, F; nmr \\ 27 & CHCLOCF2CHF & 173 & 1.4520 & C, H \\ 28 & CHCLOCF2CHF & 173 & 1.4520 & C, H \\ 29 & CF2CHOCHC & 173 & 1.4520 & C, H, F; nmr \\ 20 & CNOCF2CHF & 165 & 1.3803 & C, H, F; nmr \\ 20 & CF2CHOCHC & 173 & 1.4520 & C, H, F; nmr \\ 20 & CH2COF2CHF & 165 & 1.3801 & C, H, F; nmr \\ 20 & CH2COF2CHF & 165 & 1.3800 & C, H, F; nmr \\ 20 & CF2CHOCHC & 174 & 1.3810 & C, H, F; nmr \\ 20 & CH2CH2CHF & 165 & 1.3803 & C, H, F; nmr \\ 20 & CF2CHOCHF & 112 & 1.3880 & C, H, F; nmr \\ 20 & CF2CHOCHF & 37 & 1.3300 & C, H, F; nmr \\ 20 & CF2CHOCHF & 37 & 1.3300 & C, H, F; nmr \\ 20 & CF2CHOCHF & 45.5 & 1.3002 & C, H, F; nmr \\ 30 & CF2CHOCHF & 53 & 1.3300 & C, H, F; nmr \\ 30 & CF2CHOCHF & 53 & 1$						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					C, H; nmr	Deep anesthesia at 1.5%
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			118			Too unstable to test
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			62(50)	1,4089		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				1.3982	C, H, F; nmr	Toxic convulsant
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			69(50)			Convulsant at 0.6%
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						Good anesthetic at 2.5%
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				1.4130		Too unstable to test
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						Anesthetic, toxic
15 CH;ClOCF;CHClr 144 1.4187 C, H Too unstable to test 16 CHCl_OCF;CHClr 154 1.4264 C, H Too unstable to test 17 CH;ClOCF;CCL 157 1.4326 C, H; nmr Too unstable to test 18 CCLOCF;CHCl 172 1.4440 C, H; nmr Too unstable to test 20 CCLOCF;CCL 48 (5) 1.4551 C, F Scattive, some ataxia 21 CH;OCF;CHF; 77 1.3287 C, H Too unstable to test 23 CHCLOCF;CHF; 77 1.3287 C, H Too unstable to test 24 CCLOCF;CHF; 85.5 1.3493 C, H, F; nmr Too unstable to test 25 CCLOCF;CHF; 105 1.3730 C, H, F Good anesthetic at 1.25% 25 CHCLOCF;CHBrCl 124 1.4183 C, H, CI Too unstable to test 26 CH;OCF;CHCl; 173 1.4520 C, H, F; nmr Too unstable to test 27 CHCLOCF;CBrCl; 174 1.3630 C, H, F; nmr Too unstable to test 28 CH			66(20)		C, F	Sedative, some ataxia
16 CHCloOCF,CCL 154 1.4264 C, H Too unstable to test 17 CH ₄ ClOCF,CCL 157 1.4326 C, H; nmr Too unstable to test 18 CClOCF,CCL 172 1.4440 C, H; nmr Too unstable to test 19 CHClOCF,CCL 166 1.4382 C, H; nmr Too unstable to test 20 CClOCF,CCL 48 (5) 1.4551 C, F Sedative, some atxia 21 CH ₅ OCF,CCL 77 1.3287 C, H Deep anesthesia at 1.25% 22 CH ₅ OCF,CHF; 77 1.3287 C, H Deep anesthesia at 1.25% 23 CHCl ₅ OCF,CHF; 105 1.3730 C, H, F; nmr Good anesthetic at 1.25% 24 CCl ₅ OCF,CBrCL 124 1.4183 C, H, F; nmr Too unstable to test 25 CCl ₅ OCF,CBrCL 173 1.4520 C, H, F; nmr Too unstable to test 28 CHCl ₅ OCF,CBrCL 174 1.4382 C, H, F; nmr Too unstable to test 29 CF ₅ CH ₂ OCH,4 31.2 1.2942 Weak anesthetic at 1.9%; irrinting 2				1.3861		Anesthetic at 1.25%
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			144			Too unstable to test
$\begin{array}{cccccccccccccccccccccccccccccccccccc$			154	1.4264		Too unstable to test
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				1.4326		Too unstable to test
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\rm CCl_3OCF_2CHCl_2$	172	1,4440	C, H; nmr	Too unstable to test
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\mathrm{CHCl_2OCF_2CCl_3}$	166	1,4382	C, H; nmr	Too unstable to test
22CH _c ClOCF ₄ CHF ₂ 771.3287C, HToo unstable to test23CH _c loCF ₅ CHF ₂ 85.51.3493C, HDeep anesthesia at 1.25%24CCh ₀ CF ₅ CHF ₂ 1051.3730C, H, F; nmrGood anesthetic at 5%25CCh ₀ CF ₅ CHF ₂ 1121.3815C, FConvulsant at 1.25%26CH ₀ CF ₇ CHBrCl ^p 1241.4183C, H, F; nmrToo unstable to test27CHCh ₀ CF ₇ CHBrCl ₂ 1861.4640C, H, F; nmrToo unstable to test28CHCl ₀ OCF ₄ CBrCl ₂ 1861.4640C, H, F; nmrToo unstable to test30CF ₂ CH ₂ OCH ₄ Cl771.3340C, H, ClToo unstable to test31CF ₄ CH ₀ OCH ₂ L911.3658C, H, FAnesthetic at 1.9%; irritating32CF ₄ CHCOCHCl ₂ 1121.3882C, H, F; nmrToo unstable to test33CF ₄ CH ₂ OCHF ₄ 63 (75)1.4046C, H; F; nmrToo unstable to test34CF ₄ CH ₂ OCHF ₄ 37C, H, F; nmrToo unstable to test35CF ₄ CH ₂ OCHF ₄ 48.51.3002C, H, F; nmrToo unstable to test36CF ₄ CH ₀ OCHF ₄ 37C, H, F; nmrToo unstable to test37CF ₄ CH ₀ OCHF ₄ 37C, H, F; nmrToo unstable to test38CF ₄ CH ₂ OCHF ₄ 48.51.3002C, H, FGood anesthetic at 5%39CF ₄ CH ₀ OCHF ₄ 37C, H, ClWeak anesthetic at 5%40			48(5)	1.4551	C, F	Sedative, some ataxia
23 CHCl ₂ OCF ₂ CHF ₂ 85.5 1.3493 C, H Deep anesthesia at 1.25% 24 CCl ₃ OCF ₂ CHF ₂ 105 1.3730 C, H, F; mm Good anesthetic at 5% 25 CCl ₃ OCF ₂ CHF ₂ 112 1.3815 C, F Convulsant at 1.25% 26 CH ₃ OCF ₂ CHF ₁ 124 1.4183 C, H, F; mm Too unstable to test 27 CHCl ₂ OCF ₂ CHBrCl 173 1.4520 C, H, F; mm Too unstable to test 29 CF ₃ CH ₂ OCH ₂ 186 1.4640 C, H, F; mm Too unstable to test 30 CF ₃ CH ₂ OCH ₂ Cl 77 1.3340 C, H, F; mm Too unstable to test 31 CF ₃ CH ₂ OCH ₂ Cl 112 1.3858 C, H, F; mm Too unstable to test 33 CF ₄ CH ₂ OCCl ₅ 106 1.3861 C, H, F; mm Too unstable to test 34 CF ₃ CH ₄ OCCl ₅ 106 1.3850 C, H, F me toustable to test 35 CF ₄ CH ₂ OCCl ₅ 106 1.3851 C, H, F; mm Too unstable to test 10% 36 CF ₄ CH ₂ OCCF ₂ 37 C, H		$\rm CH_3OCF_2CHF_2'$	36.5	1.2939		Convulsant at 2.5%
24 CCl ₃ OCF ₂ CHF ₂ 105 1.3730 C, H, F; nmr Good anesthetic at $5/c$ 25 CCl ₃ OCF ₂ CHF ₂ 112 1.3815 C, F Convulsant at $1.25/c$ 26 CH ₃ OCF ₂ CHBrCl ^µ 124 1.4183 C, H, F Good anesthetic at $1.25/c$ 27 CHCl ₂ OCF ₂ CHBrCl ^µ 186 1.4640 C, H, F; nmr Too unstable to test 28 CHCl ₂ OCF ₂ CBrCl ₂ 186 1.4640 C, H, F; nmr Too unstable to test 29 CF ₃ CH ₂ OCH ₂ Cl 77 1.3340 C, H, Cl Too unstable to test 30 CF ₄ CH ₂ OCHCl ₂ 91 1.3658 C, H, F; nmr Too unstable to test 31 CF ₃ CH ₂ OCHCl ₂ 91 1.3683 C, H, F; nmr Too unstable to test 33 CF ₃ CH ₂ OCHCl ₂ 112 1.3882 C, H, F; nmr Too unstable to test 34 CF ₃ CHClOCCl ₃ 106 1.3861 C, H, F; nmr Toxic convulsant 35 CF ₄ CH ₄ OCHF ₂ 29 1.2653 C, H, F Cood anesthetic at $2.5/c$ 37 CF ₃ CH ₂ OCCHF ₂ 37 C		$\rm CH_2 ClOCF_2 CHF_2$ ^c	77	1.3287	С, Н	Too unstable to test
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	23	$\mathrm{CHCl_2OCF_2CHF_2}$	85.5	1.3493	С, Н	Deep anesthesia at 1.25%
25 CC4oCF_{2}CHF_{2} 112 1.3815 C, F Convulsant at 1.25% 26 CH_{a}OCF_{2}CHBrCl 124 1.4183 C, H, F Good anesthetic at 1.25% 27 CHC4_0CF_{2}CHBrCl 173 1.4520 C, H, F; nmr Too unstable to test 28 CHC1_0CF_{2}CBrCl_{2} 186 1.4640 C, H, F; nmr Too unstable to test 29 CF_{3}CH_{2}OCH_{4}^{A} 31.2 1.2942 Weak anesthetic 30 CF_{3}CH_{2}OCH_{2}CI 77 1.3340 C, H, CI Too unstable to test 31 CF_{3}CH_{4}OCHCL 91 1.3658 C, H, F; nmr Too unstable to test 31 CF_{3}CH_{4}OCCL_{4} 106 1.3861 C, H, F; nmr Too unstable to test 33 CF_{3}CH_{4}OCCL_{4} 63 (75) 1.4046 C, H, F; nmr Too unstable to test 34 CF_{3}CH_{4}OCHF_{2} 29 1.2553 C, H, F Net convalsant at $5\zeta_{i}$ 35 CF_{4}CH_{4}OCHF_{2} 48.5 1.3002 C, H, F Anesthetic at $2.5\zeta_{i}$ 36 CF_{2}CH_{4}OCHF_{2} 48.5 1.3290 C, Cl <td>24</td> <td>$\rm CCl_3OCF_2CHF_2$</td> <td>105</td> <td>1.3730</td> <td>C, H, F; nmr</td> <td>Good anesthetic at 5%</td>	24	$\rm CCl_3OCF_2CHF_2$	105	1.3730	C, H, F; nmr	Good anesthetic at 5%
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\mathrm{CCl_3OCF_2CClF_2}$	112	1.3815	C, F	
27CHCl ₂ OCF ₂ CHBrCl1731.4520C, H, F; nmrToo unstable to test28CHCl ₂ OCF ₂ CBrCl ₂ 1861.4640C, H, F; nmrToo unstable to test29CF ₃ CH ₂ OCH ₃ ^A 31.21.2942Weak anesthetic30CF ₃ CH ₂ OCHCl ₂ 771.3340C, H, ClToo unstable to test31CF ₃ CH ₂ OCHCl ₂ 911.3658C, H, FAnesthetic at $1.9\zeta_i$; irritating32CF ₃ CHClOCHCl ₂ 1121.3882C, H, F; nmrToo unstable to test33CF ₃ CH ₂ OCCl ₃ 1061.3861C, H; r, nmrToo unstable to test34CF ₃ CH ₂ OCHF ₂ 291.2653C, H, FVery weak anesthetic at $10\zeta_i$ 35CF ₄ CH ₂ OCHF ₂ 48.51.3002C, H, FVery weak anesthetic at $2.5\zeta_i$ 36CF ₃ CH ₂ OCHF ₂ 60.51.3250C, H, FAnesthetic at $5\zeta_i$ 39CF ₃ CH ₂ OCHF ₂ 74.51.3439C, ClConvulsant at $5\zeta_i$ 40CF ₃ CHBrOCHF ₂ 64.51.3297C, HLight anesthetia at $12.5\zeta_i$ 41CF ₃ CH ₂ OCF ₂ CHF ₂ 28C, H; nmrNot anesthetic at $5\zeta_i$ 42CHF ₂ OCF ₂ CHF ₂ 28C, H; nmrNot anesthetic at $5\zeta_i$ 44CHF ₂ OCF ₂ CHF ₂ 28C, H; nmrNot anesthetic at $5\zeta_i$ 44CHF ₂ OCF ₂ CHF ₂ 55.51.3030C, HGood anesthetic at $1.9\zeta_i$ 45CHF ₂ OCF ₂ CHF ₂ 55.51.3030C, H, FAnesthetic at $2.5\zeta_i$ </td <td>26</td> <td>$CH_3OCF_2CHBrCl^{g}$</td> <td>124</td> <td>1.4183</td> <td>С, Н, F</td> <td></td>	26	$CH_3OCF_2CHBrCl^{g}$	124	1.4183	С, Н, F	
28CHCl_0CF_2CBrCl_21861.4640C, H, F; nmrToo unstable to test29CF_3CH_0CH_40CH31.21.2942Weak anesthetic30CF_3CH_0CH_2CI771.3340C, H, CIToo unstable to test31CF_3CH_0CHCL2911.3658C, H, FAnesthetic at $1.9\zeta_4$; irritating32CF_3CHCIOCHCL21121.3882C, H, F; nmrToo unstable to test33CF_4CH_0CCG63 (75)1.4046C, H, F; nmrToo unstable to test34CF_3CHCIOCHCL2291.2653C, H, FVery weak anesthetic at $10\zeta_4$ 35CF_4CH_0CHF2291.2653C, H, FVery weak anesthetic at $2.5\zeta_4$ 36CF_3CHCIOCHF237C, H, F; nmrConvulsant at $5\zeta_4$ 37CF_3CH_0CCIF237C, H, F; nmrConvulsant at $5\zeta_4$ 38CF_4CL0CHF2531.3142C, H, GIWeak anesthetic at $5\zeta_4$ 40CF_3CHBOCHF264.51.3297C, HConvulsant at $5\zeta_6$ 41CF_4CHBOCHF228.5C, H; nmrNot anesthetic at $1\zeta_6$ 42CHF_4OCF_4CHF228C, H; nmrNot anesthetic at $1\zeta_6$ 44CHF_4OCF_4CHF228C, H; nmrNot anesthetic at $5\zeta_6$ 43CHF_4OCF_4CHF228.5C, H; nmrNot anesthetic at $5\zeta_6$ 44CHF4OCF4CHF228.5C, H; nmrNot anesthetic at $1\zeta_6$ 45CHF4OCF4CHF256.51.3030C, H, FAnesthetic at $2.5\zeta_6$ 4	27	$\mathrm{CHCl_2OCF_2CHBrCl}$	173	1.4520	C, H, F; nmr	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	28	$\mathrm{CHCl_2OCF_2CBrCl_2}$	186	1.4640		Too unstable to test
31 $CF_3CH_2OCHCl_2$ 911.3658C, H, FAnesthetic at 1.9% ; irritating32 $CF_3CHClOCHCl_2$ 1121.3882C, H, F; nmrToo unstable to test33 $CF_3CH_2OCCl_5$ 1061.3861C, H, F; nmrToo unstable to test34 $CF_3CHClOCCl_5$ 63 (75)1.4046C, H; nmrToxic convulsant35 $CF_4CH_2OCHF_2$ 291.2653C, H, FVery weak anesthetic at 10% 36 $CF_3CHClOCHF_2$ 48.51.3002C, H, FGood anesthetic at 2.5% 37 $CF_3CH_2OCCHF_2$ 37C, H, F; nmrConvulsant at 5% 38 $CF_3CLCl_2OCHF_2$ 60.51.3250C, H, FAnesthetic at 5% 39 $CF_3CHClOCCIF_2$ 74.51.3439C, ClConvulsant at 5% 40 $CF_3CCl_2OCHF_2$ 64.51.3297C, HLight anesthetic at $1.2.5\%$ 41 $CF_3CHBrOCHF_2$ 28.5C, H; nmrNot anesthetic at 5% 42 $CHF_2OCF_2CHF_2$ 28C, H; nmrNot anesthetic at 5% 44 $CHF_2OCF_2CHF_2$ 28C, H; nmrNot anesthetic at 5% 45 $CHF_2OCF_2CHF_5$ 56.51.3030C, HGood anesthetic at 1.9% 46 $CHF_2OCF_2CHF_5$ 56.51.3030C, H, F; nmrDeep anesthesia at 2.5% 47 CHF_2OCF_4CHCIF 551.5266C, H, F; nmrDeep anesthesia at 2.5% 48 CHF_2OCF_4CHCIF 551.3030C, H, FAnesthetic at 2.5% 49 C	29	$\mathrm{CF_3CH_2OCH_3}^h$	31.2	1.2942		Weak anesthetic
31 $CF_3CH_2OCHCl_2$ 911.3658C, H, FAnesthetic at 1.9% ; irritating32 $CF_3CHClOCHCl_2$ 1121.3882C, H, F; nmrToo unstable to test33 $CF_3CH_2OCCl_3$ 1061.3861C, H, F; nmrToo unstable to test34 $CF_3CHClOCCl_3$ 63 (75)1.4046C, H; nmrToxic convulsant35 $CF_3CH_2OCHF_2$ 291.2653C, H, FVery weak anesthetic at 10% 36 $CF_3CHClOCHF_2$ 48.51.3002C, H, FGood anesthetic at 2.5% 37 $CF_3CH_2OCCIF_2$ 37C, H, F; nmrConvulsant at 5% 38 $CF_4CCl_2OCHF_2$ 60.51.3250C, H, FAnesthetic at 5% 39 $CF_3CHClOCCIF_2$ 531.3142C, H, ClWeak anesthetic at 5% 40 $CF_3CCl_2OCCIF_2$ 74.51.3439C, ClConvulsant at 5% 41 $CF_3CHBrOCHF_4$ 64.51.3297C, HGood anesthetic at $1.2.5\%$ 43 $CHF_4OCF_4CIF_2$ 28.5C, H; nmrNot anesthetic at 5% 44 $CHF_2OCF_4CIF_2$ 28C, H; nmrNot anesthetic at 5% 45 $CHF_4OCF_4CIF_5$ 56.51.3030C, HGood anesthetic at 1.9% 46 $CHF_4OCF_4CIF_5$ 56.51.3030C, H, F; nmrDeep anesthesia at 2.5% 47 $CHF_4OCF_4CIF_5$ 56.51.3235C, H, F; nmrDeep anesthetic at 2.5% 48 $CHF_4OCF_4CCHF_2$ 551.2966C, HVery weak anesthetic at 2.5% </td <td>30</td> <td>$CF_{3}CH_{2}OCH_{2}Cl$</td> <td>77</td> <td>1.3340</td> <td>C, H, Cl</td> <td>Too unstable to test</td>	30	$CF_{3}CH_{2}OCH_{2}Cl$	77	1.3340	C, H, Cl	Too unstable to test
32CF_3CHClOCHCl21121.3882C, H, F; nmrToo unstable to test33CF_5CH2OCCl31061.3861C, H, F; nmrToo unstable to test34CF_5CHClOCCl363 (75)1.4046C, H; nmrToxic convulsant35CF_4CH2OCHF2291.2653C, H, FVery weak anesthetic at 10%36CF_3CHClOCHF248.51.3002C, H, FGood anesthetic at 2.5%37CF_3CH2OCCIF237C, H, F; nmrConvulsant at 5%38CF_6CL2OCHF260.51.3250C, H, FAnesthetic at 5%40CF_6CCl2OCHF2531.3142C, H, ClWeak anesthetic at 5%41CF_6CHBrOCHF264.51.3297C, HGood anesthetic at 5%42CHF4OCF2CHF228.5C, H; nmrNot anesthetic at 5%43CHF4OCF2CHF228.5C, H; nmrNot anesthetic at 5%44CHF4OCF2CHCIF456.51.3030C, HGood anesthetic at 5%45CHF4OCF2CHCIF456.51.3030C, H, FAnesthetic at 5%46CHF4OCF2CBrCIF831.3510C, H, FAnesthetic at 2.5%47CHF4OCF2CBrCIF831.3510C, H, FAnesthetic at 2.5%48CHF4OCF2CBrCIF5551.22066C, H, FAnesthetic at 2.5%49CHF4CHCIOCHF2741.3351C, H, FAnesthetic at 1.5%49CHF4CHCIOCHF250.2Good anesthetic at 1.5%Good anesthetic at 2.5%50 <td>31</td> <td>$CF_3CH_2OCHCl_2$</td> <td>91</td> <td>1.3658</td> <td></td> <td>Anesthetic at 1.9%; irritating</td>	31	$CF_3CH_2OCHCl_2$	91	1.3658		Anesthetic at 1.9%; irritating
33 $CF_3CH_2OCC_{13}$ 1061.3861C, H, F; nmrToo unstable to test34 $CF_3CHClOCC_{13}$ 63 (75)1.4046C, H; nmrToxic convulsant35 $CF_3CHClOCH_{2}$ 291.2653C, H, FVery weak anesthetic at 10%36 $CF_3CHClOCHF_2$ 48.51.3002C, H, FGood anesthetic at 2.5%37 $CF_3CH_2OCClF_2$ 37C, H, F; nmrConvulsant at 5%38 $CF_4CCl_2OCHF_2$ 60.51.3250C, H, FAnesthetic at 5%39 $CF_4CHClOCClF_2$ 531.3142C, H, ClWeak anesthetic at 5%40 $CF_4CCl_4OCClF_2$ 74.51.3297C, HGood anesthetic at 5%41 $CF_4CH_FOCF_2CHF_2$ 28.5C, H; nmrNot anesthetic at 5%42 $CHF_2OCF_2CHF_2$ 28C, H; nmrNot anesthetic at 5%43 $CHF_2OCF_2CHF_2$ 28C, H; nmrNot anesthetic at 5%44 $CHF_2OCF_2CHF_2$ 451.3030C, H, FAnesthetic at 5%45 $CHF_2OCF_2CHCIF^{\prime}$ 56.51.3030C, H, Good anesthetic at 5%46 $CHF_2OCF_2CHCIF^{\prime}$ 56.51.3030C, H, FAnesthetic at 2.5%47 $CHF_2OCF_2CHCIF_4$ 551.2966C, H, F; nmrDeep anesthesia at 2.5%48 $CHF_2CH_4OCHF_4$ 741.3351C, H, FAnesthetic at 2.5%49 $CHF_2CHCIOCHF_4$ 50.2Good anesthetic at 2.5%50.2	32	$\rm CF_3 CHClOCHCl_2$	112	1.3882	C, H, F; nmr	
34 $CF_3CHClOCCl_3$ 63 (75)1.4046C, H; nmrToxic convulsant35 $CF_4CH_2OCHF_2$ 291.2653C, H, FVery weak anesthetic at 10% 36 $CF_3CHClOCHF_2$ 48.51.3002C, H, FGood anesthetic at 2.5% 37 $CF_3CH_2OCCIF_2$ 37C, H, F; nmrConvulsant at 5% 38 $CF_3CCI_2OCHF_2$ 60.51.3250C, H, FAnesthetic at 5% 39 $CF_3CHCIOCCIF_2$ 531.3142C, H, ClWeak anesthetic at 5% 40 $CF_3CCI_2OCCIF_2$ 74.51.3439C, ClConvulsant at 5% 41 $CF_3CHFDCHF_2$ 64.51.3297C, HGood anesthetic at 1% 42 $CHF_2OCF_2CHF_2$ 28.5C, H; nmrNot anesthetic at 5% 43 $CHF_2OCF_2CHF_2$ 28C, H; nmrNot anesthetic at 5% 44 $CHF_2OCF_2CHF_2$ 45C, H; nmrNot anesthetic at 1.9% 45 CHF_2OCF_2CHFF 641.3235C, H, FAnesthetic at 1.9% 46 CHF_2OCF_2CHFF 641.3235C, H, FAnesthetic at 2.5% 47 $CHF_2OCF_2CBrCIF$ 831.3510C, H, F; nmrDeep anesthesia at 2.5% 48 $CHF_2CH_2OCHF_2$ 551.2966C, HVery weak anesthetic at 5% 49 $CHF_2CHCIOCHF_2$ 741.3351C, H, FAnesthetic at 1.5% 50 $CF_3CHBrCl^e$ 50.2Good anesthetic at 2.5%	33	$CF_3CH_2OCCl_3$	106	1.3861	C, H, F; nmr	Too unstable to test
36 $CF_{3}CHClOCHF_{2}$ 48.51.3002C, H, FGood anesthetic at 2.5%37 $CF_{3}CH_{2}OCClF_{2}$ 37C, H, F; nmrConvulsant at 5%38 $CF_{3}CCl_{2}OCHF_{2}$ 60.51.3250C, H, FAnesthetic at 5%39 $CF_{3}CHClOCClF_{2}$ 531.3142C, H, ClWeak anesthetic at 5%40 $CF_{3}CCl_{2}OCClF_{2}$ 74.51.3439C, ClConvulsant at 5%41 $CF_{3}CHF_{0}OCF_{2}CHF_{2}$ 64.51.3297C, HGood anesthetic at 1%42 $CHF_{2}OCF_{2}CHF_{2}$ 28.5C, H; nmrNot anesthetic at 5%43 $CHF_{2}OCF_{2}ClF_{2}$ 28C, H; nmrNot anesthetic at 5%44 $CHF_{2}OCF_{2}CRF_{2}$ 45C, H; nmrNot anesthetic at 5%45 $CHF_{2}OCF_{2}CHClF'$ 56.51.3030C, H, FAnesthetic at 2.5%46 $CHF_{2}OCF_{2}CRClF_{2}$ 831.3510C, H, F; nmrDeep anesthetic at 2.5%47 $CHF_{2}OCF_{2}CBrClF$ 831.3510C, H, F; nmrDeep anesthetic at 2.5%48 $CHF_{2}OCH_{2}OCHF_{2}$ 551.2966C, HVery weak anesthetic at 5%49 $CHF_{2}CHClOCHF_{2}$ 741.3351C, H, FAnesthetic at 1.5%50 $CF_{3}CHBrCl^{4}$ 50.2Good anesthetic at 2.5%Good anesthetic at 2.5%	34	$CF_{3}CHClOCCl_{3}$	63(75)	1.4046		Toxic convulsant
36 $CF_{3}CHClOCHF_{2}$ 48.5 1.3002 C, H, F Good anesthetic at 2.5% 37 $CF_{3}CH_{2}OCClF_{2}$ 37 $C, H, F; nmr$ Convulsant at 5% 38 $CF_{3}CCl_{2}OCHF_{2}$ 60.5 1.3250 C, H, F Anesthetic at 5% 39 $CF_{3}CHClOCClF_{2}$ 53 1.3142 C, H, Cl Weak anesthetic at 5% 40 $CF_{3}CCl_{2}OCClF_{2}$ 74.5 1.3439 C, Cl Convulsant at 5% 41 $CF_{3}CHFOCHF_{2}$ 64.5 1.3297 C, H Good anesthetic at 1% 42 $CHF_{2}OCF_{2}CHF_{2}$ 28.5 C, H Light anesthesia at 12.5% 43 $CHF_{2}OCF_{2}ClF_{2}$ 28 $C, H; nmr$ Not anesthetic at 5% 44 $CHF_{2}OCF_{2}CHF_{2}$ 28.5 $C, H; nmr$ Not anesthetic at 5% 45 $CHF_{2}OCF_{2}CBrF_{2}$ 45.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_{2}OCF_{2}CRClF$ 64 1.3235 C, H, F Anesthetic at 2.5% 47 $CHF_{2}OCF_{2}CBrClF$ 83 1.3510 C, H, F Anesthetic at 2.5% 48 $CHF_{2}CH_{2}OCHF_{2}$ 55 1.2966 C, H Very weak anesthetic at 5% 49 $CHF_{2}CHClOCHF_{2}$ 74 1.3351 C, H, F Anesthetic at 1.5% 50 $CF_{3}CHBrCl^{4}$ 50.2 C, H, F C, H, F $Chethetic at 2.5\%$	35	$\rm CF_3CH_2OCHF_2$	29	1.2653	С, Н, F	Very weak anesthetic at 10%
37 $CF_3CH_2OCClF_2$ 37 $C, H, F; nmr$ Convulsant at $5\zeta_{\ell}$ 38 $CF_3CCl_2OCHF_2$ 60.5 1.3250 C, H, F Anesthetic at $5\zeta_{\ell}$ 39 $CF_3CHClOCClF_2$ 53 1.3142 C, H, Cl Weak anesthetic at $5\zeta_{\ell}$ 40 $CF_3CCl_2OCClF_2$ 74.5 1.3439 C, Cl Convulsant at $5\zeta_{\ell}$ 41 $CF_3CHBrOCHF_2$ 64.5 1.3297 C, H Good anesthetic at $1\zeta_{\ell}$ 42 $CHF_2OCF_2CHF_2$ 28.5 C, H Light anesthesia at $12.5\zeta_{\ell}$ 43 $CHF_2OCF_2CBrF_2$ 28 $C, H; nmr$ Not anesthetic at $5\zeta_{\ell}$ 44 $CHF_2OCF_2CBrF_2$ 45 $C, H; nmr$ Not anesthetic at $5\zeta_{\ell}$ 45 $CHF_2OCF_2CHClF^{\ell}$ 56.5 1.3030 C, H Good anesthetic at $1.9\zeta_{\ell}$ 46 $CHF_2OCF_2CBrClF$ 64 1.3235 C, H, F Anesthetic at $2.5\zeta_{\ell}$ 47 $CHF_2OCF_2CBrClF$ 83 1.3510 $C, H, F; nmr$ Deep anesthesia at $2.5\zeta_{\ell}$ 48 $CHF_2CH_2OCHF_2$ 55 1.2966 C, H Very weak anesthetic at $5\zeta_{\ell}$ 49 $CHF_2CHClOCHF_2$ 74 1.3351 C, H, F Anesthetic at $1.5\zeta_{\ell}$ 50 $CF_3CHBrCl^4$ 50.2 C, H, F Anesthetic at $2.5\zeta_{\ell}$	36	$CF_3CHClOCHF_2$	48.5	1.3002	С, Н, Г	Good anesthetic at 2.5%
38 $CF_4CCl_2OCHF_2$ 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 $CHF_2OCF_2CBrF_2$ 28 C, H; nmr Not anesthetic at 5% 44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at 5% 45 $CHF_2OCF_2CHCIF^i$ 56.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_2OCF_2CBrCIF$ 64 1.3235 C, H, F Anesthetic at 2.5% 47 $CHF_2OCF_2CBrCIF$ 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 $CHF_2CHCIOCHF_2$ 74 1.3351 C, H, F Anesthetic at 1.5%	37	$CF_3CH_2OCClF_2$	37		C, H, F; nmr	
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 $CHF_2OCF_2ClF_2$ 28 C, H; nmr Not anesthetic at 5% 44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at 5% 45 $CHF_2OCF_2CHClF^{\ell}$ 56.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_2OCF_2CBrClF$ 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 $CF_3CHBrCl^4$ 50.2 $CHF_2CHClOCHF_2$ 50.2 $CHF_2CHCLOCHF$	38	$\rm CF_3CCl_2OCHF_2$	60.5	1.3250	С, Н, F	
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 $CHF_2OCF_2ClF_2$ 28 C, H; nmr Not anesthetic at 5% 44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at 5% 45 $CHF_2OCF_2CHClF^{\ell}$ 56.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_2OCF_2CRl_2F$ 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 $CHF_2OCH_2OCHF_2$ 55 1.2966 C, H, F Anesthetic at 1.5% 49 $CHF_2CHClOCHF_2$ 74 1.3351 C, H, F Anesthetic at 1.5% 50 $CF_3CHBrCl^4$ 50.2 Good anesthetic at 2.5% Good anesthetic at 2.5%	39	$CF_3CHClOCClF_2$	53			
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 $CHF_2OCF_2CCF_2$ 28 C, H; nmr Not anesthetic at 5% 44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at 5% 45 $CHF_2OCF_2CHCIF^i$ 56.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_2OCF_2CR_2F$ 64 1.3235 C, H, F Anesthetic at 2.5% 47 $CHF_2OCF_2CBrCIF$ 83 1.3510 C, H, F; nmr Deep anesthesia at 2.5% 48 $CHF_2OCH_2OCHF_2$ 55 1.2966 C, H, F Anesthetic at 1.5% 49 $CHF_2CHCIOCHF_2$ 74 1.3351 C, H, F Anesthetic at 1.5% 50 $CF_3CHBrCl^4$ 50.2 50.2 $CHF_2CHCIOCHF_2$ 50.2	40	$CF_3CCl_2OCClF_2$	74.5	1.3439		· · · · · · · · · · · · · · · · · · ·
42 $CHF_2OCF_2CHF_2$ 28.5 C, H Light anesthesia at 12.5% 43 $CHF_2OCF_2CCIF_2$ 28 C, H; nmr Not anesthetic at 5% 44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at 5% 45 $CHF_2OCF_2CHCIF^i$ 56.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_2OCF_2CR_2F$ 64 1.3235 C, H, F Anesthetic at 2.5% 47 $CHF_2OCF_2CBr_2F$ 83 1.3510 C, H, F; nmr Deep anesthesia at 2.5% 48 $CHF_2OCH_2OCHF_2$ 55 1.2966 C, H Very weak anesthetic at 5% 49 $CHF_2CHCIOCHF_2$ 74 1.3351 C, H, F Anesthetic at 1.5% 50 $CF_3CHBrCl^e$ 50.2 Good anesthetic at 2.5% Good anesthetic at 2.5%	41	$CF_{3}CHBrOCHF_{2}$	64.5	1.3297		Good anesthetic at 1%
43 $CHF_2OCF_2CCIF_2$ 28 C, H; nmr Not anesthetic at 5% 44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at 5% 45 $CHF_2OCF_2CHCIF^i$ 56.5 1.3030 C, H Good anesthetic at 1.9% 46 $CHF_2OCF_2CR_2FF$ 64 1.3235 C, H, F Anesthetic at 2.5% 47 $CHF_2OCF_2CBr_2FF$ 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 $CHF_2CHCIOCHF_2$ 74 1.3351 C, H, F Anesthetic at 1.5% 50 $CF_3CHBrCl^e$ 50.2 Good anesthetic at 2.5%	42					
44 $CHF_2OCF_2CBrF_2$ 45 C, H; nmr Not anesthetic at $5\frac{1}{6}$ 45 $CHF_2OCF_2CHClF^i$ 56.5 1.3030 C, H Good anesthetic at $1.9\frac{1}{6}$ 46 $CHF_2OCF_2CCl_2F$ 64 1.3235 C, H, F Anesthetic at $2.5\frac{1}{6}$ 47 $CHF_2OCF_2CBrClF$ 83 1.3510 C, H, F; nmr Deep anesthesia at $2.5\frac{1}{6}$ 48 $CHF_2CH_2OCHF_2$ 55 1.2966 C, H Very weak anesthetic at $5\frac{1}{6}$ 49 $CHF_2CHClOCHF_2$ 74 1.3351 C, H, F Anesthetic at $1.5\frac{1}{6}$ 50 $CF_3CHBrCl^4$ 50.2 Good anesthetic at $2.5\frac{1}{6}$ Good anesthetic at $2.5\frac{1}{6}$	43	$\mathrm{CHF}_{2}\mathrm{OCF}_{2}\mathrm{CClF}_{2}$	28			
46 CHF ₂ OCF ₂ CCl ₂ F 64 1.3235 C, H, F Anesthetic at 2.5% 47 CHF ₂ OCF ₂ CBrClF 83 1.3510 C, H, F; mmr Deep anesthesia at 2.5% 48 CHF ₂ CH ₂ OCHF ₂ 55 1.2966 C, H Very weak anesthetic at 5% 49 CHF ₂ CHClOCHF ₂ 74 1.3351 C, H, F Anesthetic at 1.5% 50 CF ₃ CHBrCl ^e 50.2 Good anesthetic at 2.5%	44	$\mathrm{CHF_{2}OCF_{2}CBrF_{2}}$	45			Not an sthetic at 5%
46 CHF2OCF2CCl2F 64 1.3235 C, H, F Anesthetic at 2.5% 47 CHF2OCF2CBrClF 83 1.3510 C, H, F; nmr Deep anesthesia at 2.5% 48 CHF2CH2OCHF2 55 1.2966 C, H Very weak anesthetic at 5% 49 CHF2CHClOCHF2 74 1.3351 C, H, F Anesthetic at 1.5% 50 CF3CHBrCl ^e 50.2 Good anesthetic at 2.5%	4.5			1.3030		
47 $CHF_2OCF_2CBrClF$ 831.3510C, H, F; nmrDeep anesthesia at 2.5%48 $CHF_2CH_2OCHF_2$ 551.2966C, HVery weak anesthetic at 5%49 $CHF_2CHClOCHF_2$ 741.3351C, H, FAnesthetic at 1.5%50 $CF_3CHBrCl^e$ 50.2Good anesthetic at 2.5%	46					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						
49 $CHF_2CHClOCHF_2$ 741.3351C, H, FAnesthetic at 1.5% 50 $CF_3CHBrCl^e$ 50.2Good anesthetic at 2.5%						
50 $CF_3CHBrCl^2$ 50.2 Good anesthetic at 2.5 $\frac{C}{C}$						
	50					
	51	CF ₃ CH ₂ OCH=CH ₂ ^e				

 TABLE I

 PROPERTIES OF HALOGENATED METHYL ETHYL ETHERS

^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 $\pm 0.4\%$ 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). ^e 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 OCHF₂ group is also less reactive than OCF₂-CHClF or OCF₂CHF₂ 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-

$$\begin{array}{ccc} \mathrm{CHF_2OCF_2CHF_2} &\longrightarrow & \mathrm{CHF_2OCF_2CClF_2} \\ & \mathbf{42} & \mathbf{43}, \ 80\% \\ \mathrm{CHF_2OCF_2CHClF} &\longrightarrow & \mathrm{CHF_2OCF_2CCl_2F} \\ & \mathbf{45} & \mathbf{46}, \ 80\% \end{array}$$

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

 $\begin{array}{c} \mathrm{CHF_2OCF_2CHF_2} \longrightarrow \mathrm{CHF_2OCF_2CBrF_2} \\ \mathbf{42} & \mathbf{44} \ (25\% \ \mathrm{conversion}, \ 60\% \ \mathrm{yield}) \\ \mathrm{CHF_2OCF_2CHClF} \longrightarrow \mathrm{CHF_2OCF_2CBrClF} \\ \mathbf{45} & \mathbf{47} \ (60\% \ \mathrm{conversion}, \ 70\% \ \mathrm{yield}) \\ \mathrm{CF_3CH_2OCHF_2} \longrightarrow \mathrm{CF_3CHBrOCHF_2} \end{array}$

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 K₂CO₃. 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 CF₃CHBrCl and CF₃CH₂OCH=CH₂ 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 reported⁶⁻⁸ and other studies are in progress.

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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 O₂.⁹ 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 distu or by the Siwoloboff method and are uncorr. Nmr spectra were detd in CCl₄ (Me₄Si) using a Varian A-60 spectrophotometer.

Compds 1, 8, 14, 21, 29, 42, and 45 were prepared according to published procedures, 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.

CF₃CH₂OCHF₂ (35) and CHF₂OCH₂CHF₂ (48).—Into the stainless steel liner of a 1-l. autoclave was placed a solu of 60 g (1 mole) of KOH pellets in 374 g (3.7 moles) of CF₃CH₂OH 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 CHClF₂ 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 CF₃CH₂OCHF₂ (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 diffuorochloromethane and 16 g more of CF₃CH₂OCHF₂. The combined product, 65 g, represents a 56.5% conversion of CHClF₂.

 $CHF_2OCH_2CHF_2$ 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 H₂O. 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 $450-475^{\circ}$. 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).