once from EtOH, gave 0.90 g (27.5%), the salt mp 210–212° dec. *Anal.* ($C_{14}H_{14}ClNO_4S$) C, H, Cl, N, S.

3-Benzoyl-4-chlorobenzenesulfonyl Chloride (15).—To a cold soln (0–5°) of 23.8 g of (0.073 mole) of 2-chloro-5-aminobenzophenone in 73 ml of AcOH and 25 ml of concd HCl was added slowly 5.58 g (0.685 mole) of $NaNO_2$ in 9.5 ml of H_2O. This mixt was stirred for 0.5 hr at 0–5°. Then was added 17.3 g (0.27 mole) of SO_2 in 51 ml of AcOH contg 2.9 g (0.017 mole) of $CuCl_2$ in 5.2 ml of H_2O. This mixt was allowed to warm to room temp with stirring during 1 hr and poured into ice water. The solid was collected yielding 21.27 g (92.5%) of pale yellow solid, mp 86.5–89°. A sample was recrystd from methylcyclohexane, mp 90.5–92°. *Anal.* ($C_{13}H_8Cl_2O_3S$) C, H, Cl, S.

1,3-Dihydro-7-(methanesulfonamido)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (16).—To a slurry of 2.65 g (0.01 mole) of 7-amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[11] in 20 ml of dry pyridine was added portionwise 1.37 g (0.012 mole) of $MeSO_2Cl$. The mixt was stirred for 1.0 hr at room temp and then warmed on a steam bath for 0.5 hr. Evapn of the reaction mixt *in vacuo* gave a syrup which was taken up in $CHCl_3$, washed (H_2O), dried ($MgSO_4$), and reevapd to give 4.3 g of syrup which crystd from PhH giving 3.01 g of yellow crystals, mp 149–151.5°. Two recrystns, once from EtOAc and once from EtOH, yielded 1.55 g (45%) of nearly white crystals, mp 192–193° dec. *Anal.* ($C_{17}H_{17}N_3O_3S$) C, H, N, S.

1,3-Dihydro-1-methyl-7-(*N*-methylmethanesulfonamido)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (17).—A soln of 1.88 g (0.0055 mole) of **16** in 35 ml of MeOH was converted to the Na salt with 1.4 g (0.0066 mole) of 25% NaOMe and evapd to dryness *in vacuo*. The residue was dissolved in 30 ml of DMF and 1.5 ml of MeI was added dropwise with stirring for 2.0 hr at room temp. The soln was poured into 300 ml of ice water giving 1.45 g of solid, mp 162–166° dec. Recrystn from *i*-PrOH gave 1.25 g (70.5%) of nearly white crystals, mp 174–176° dec. *Anal.* ($C_{18}H_{19}N_3O_3S$) C, H, N, S.

(11) O. Keller, N. Steiger, and L. H. Sternbach, U. S. Patent 3,121,114 (1964); *Chem. Abstr.*, **61**, 1333*b* (1964).

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General Anesthetics. 2. Halogenated Methyl Isopropyl Ethers

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Twenty-two new halogenated methyl isopropyl ethers have been synthesized for evaluation as general inhalant anesthetics. Sixteen stable compounds were evaluated using mice. Twelve of these compounds had anesthetic activity but were irritating and toxic, making them unsuitable for further study or clinical trials.

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] Fluoroxene ($CF_3CH_2OCH{=}CH_2$), halothane ($CF_3CHClBr$), and methoxyflurane ($CH_3OCF_2CHCl_2$) are presently in clinical use.

The synthesis and pharmacological properties of some methyl ethyl ethers have been reported recently.[4,5] We have continued this investigation by synthesizing 22 new halogenated methyl isopropyl ethers; 16 of these have been evaluated as general anesthetics in mice (Table I). The remaining were too unstable to test.

Synthesis.—The chloro compounds were synthesized by photochlorination of four fluorinated isopropyl methyl ethers. Chlorination of **1**, following the published procedure,[6,7] gave only three products resulting from substitution on the methyl group. The chlorination is described as follows where the percentages in the equation represent the maximum percentage of a given product in any chlorination mixture, the maximum amount of monochloro product being formed with addition of one Cl and so forth. Neither the perhalogenated product, $(CF_3)_2CClOCCl_3$, nor any isomers with Cl on the isopropyl group were found.

$$(CF_3)_2CHOCH_3 \xrightarrow{} (CF_3)_2CHOCH_2Cl \xrightarrow{} (CF_3)_2CHOCHCl_2 \xrightarrow{} (CF_3)_2CHOCCl_3$$
1 **2**, 82% **3**, 58% **4**, 100%

Chlorination of **5** was carried only to the first step, similarly replacing only the H on the methyl group.

$$CF_3(CF_2Cl)CHOCH_3 \xrightarrow{} CF_3(CF_2Cl)CHOCH_2Cl$$
5 **6**

The isomer, $CF_3(CF_2Cl)CClOCH_3$, was prepared by chlorination of the pentafluoroisopropenyl ether. The physical properties of this dichloro ether were significantly different from those of **6**.[8]

The chlorination of **7** was similar to that of **5** and only the methyl group was chlorinated.

$$(CF_2Cl)_2CHOCH_3 \xrightarrow{} [(CF_2Cl)_2CHOCH_2Cl] \xrightarrow{} (CF_2Cl)_2CHOCHCl_2 \xrightarrow{} (CF_2Cl)_2CHOCCl_3$$
7 **8** **9**

Chlorination of **10** gave essentially only one monochloro product **11** and only one dichloro product **12**. Further chlorination gave complex mixtures of products from which three trichloro products, **13**, **14**, and **15**, and one tetrachloro product, **16**, were isolated.

Substitution of F for Cl in the ethers **3**, **4**, **8**, **12**, **13**, and **14** was done using SbF_3 or anhyd HF. $SbCl_5$ was

(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/I. 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) 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*j* (1970).

(5) R. C. Terrell, L. Speers, A. J. Szur, J. Treadwell, and T. R. Ucciardi, *J. Med. Chem.*, **14**, 517 (1971).

(6) J. D. Park, D. M. Griffin, and J. R. Lacher, *J. Amer. Chem. Soc.*, **74**, 2293 (1952).

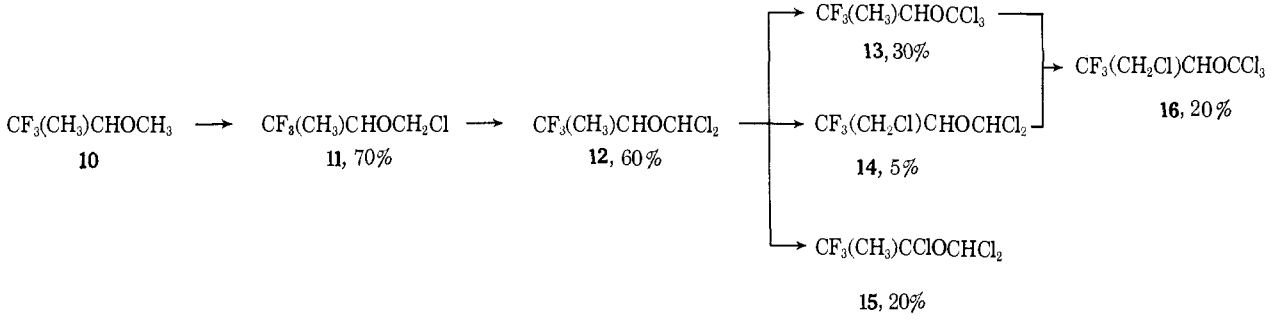
(7) J. D. Park, B. Stricklin, and J. R. Lacher, *ibid.*, **76**, 1387 (1954).

(8) Unpublished work, Air Reduction Co., 1965.

TABLE I

No.	Compd	Bp, °C (mm)	$n^{20}D$	Anal.[a]	Pharmacology
1	$(CF_3)_2CHOCH_3$	50[b]	1.2750	C, H, F	Very weak anesthetic at 2.5%,[c] excitation at 10.0%
2	$(CF_3)_2CHOCH_2Cl$[d]	78	1.3140	C, H, Cl	Good anesthesia at 1.25%, irritating
3	$(CF_3)_2CHOCHCl_2$	94	1.3385	C, H, Cl	Too unstable to test
4	$(CF_3)_2CHOCCl_3$	68 (149)	1.3575	C, H, Cl; nmr	Anesthetic at 1.25% with convulsions
5	$CF_3(CF_2Cl)CHOCH_3$	80[e]	1.3203	C, H, Cl	Anesthetic at 2.0%,[f] irritating
6	$CF_3(CF_2Cl)CHOCH_2Cl$[d]	110	1.3552	C, H, Cl	Deep anesthesia at 1.0%
7	$(CF_2Cl)_2CHOCH_3$	110	1.3636	C, H, Cl	Anesthetic at 1.0%, opisthotonus, irritating
8	$(CF_2Cl)_2CHOCHCl_2$	62 (24)	1.4071	C, H, Cl	No anesthesia at 0.6%, convulsions, toxic
9	$(CF_2Cl)_2CHOCCl_3$	44 (4)	1.4200	C, H, Cl; nmr	No anesthesia at 0.2%, toxic
10	$CF_3(CH_3)CHOCH_3$	47.8	1.3062	C, H, F	Light anesthesia at 3%
11	$CF_3(CH_3)CHOCH_2Cl$	89	1.3515	*g*	Too unstable to test
12	$CF_3(CH_3)CHOCHCl_2$	113	1.3785	C, H, F; nmr	Too unstable to test
13	$CF_3(CH_3)CHOCCl_3$	128	1.3975	C, H; nmr	Too unstable to test
14	$CF_3(CH_2Cl)CHOCHCl_2$	152	1.4130	C, H, F; nmr	Too unstable to test
15	$CF_3(CH_3)CClOCHCl_2$	131	1.3970	C, H, F; nmr	Too unstable to test
16	$CF_3(CH_2Cl)CHOCCl_3$	163	1.4260	C, H, F; nmr	Too unstable to test
17	$(CF_3)_2CHOCHFCl$[d]	67.2	1.3006	C, H, Cl	Anesthetic at 1.25%, irritating
18	$(CF_3)_2CHOCHF_2$[d]	41.5	1.2604	C, H, F	Good anesthetic at 5.0%
19	$(CF_3)_2CHOCCl_2F$	75	1.3175	C, H, Cl	Light anesthesia at 2.5%, toxic
20	$(CF_3)_2CHOCClF_2$	45	1.2770	C, H, Cl	Very light anesthesia at 7.5%, toxic
21	$(CF_2Cl)_2CHOCHF_2$	99	1.3415	C, H, Cl	Anesthesia at 1.25%, irritating, toxic
22	$CF_3(CH_3)CHOCHF_2$	48	<1.3	C, H	Anesthetic at 5.0%
23	$CF_3(CH_3)CFOCHF_2$	45	<1.3	C, H, F; nmr	Light anesthesia at 10%, convulsions
24	$CF_3(CH_3)CHOCF_3$	27	<1.3	F,[h] nmr	No anesthesia at 10%
25	$CF_3CHClBr$	50.2	1.3700		Good anesthetic at 2.5%
26	$CH_3OCF_2CHCl_2$	105	1.3861		Anesthetic at 1.25%
27	$CF_3CH_2OCH{=}CH_2$	43.7	1.3192		Good anesthetic at 7.5%

[a] Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Nmr spectra were recorded where indicated and were consistent with the assigned structures. [b] Reported bp 50–50.5° (E. E. Gilbert and B. Veldhuis, U. S. Patent 3,346,448 (to Allied Chemical Corp., New York, N. Y.), Oct 10, 1967; *Chem. Abstr.*, **68**, 12474 (1968)). [c] Reported AD_{50} = 2.23%.[b] [d] Louise S. Croix and Alex J. Szur, U. S. Patent 3,476,860 (to Air Reduction Co., Inc., New York, N. Y.), Nov 4, 1969; *Chem. Abstr.*, **72**, 54745 (1970). [e] Reported bp 70–80° (British Patent, 1141,099 (to Allied Chemical Corp., New York, N. Y.), Jan 22, 1969; *Chem. Abstr.*, **71**, 2970 (1969)). [f] Reported AD_{50} = 0.895%.[e] [g] Unstable, could be isolated in only 95% purity. [h] F: calcd, 62.5; found, 59.4 (98.7% pure).



used as catalyst.[9,10] Anhyd HF gave the best results since the degree of fluorination could be controlled by metering the HF and by titrating the liberated HCl. There was also less decomposition since the reaction could be done at lower temperatures. Fluorination of the dichloromethoxy ether **3** could be controlled to give both mono- and disubstitution products, **17** and **18**.

The trichloromethoxy ether **4** also gave mono- and disubstitution products **19** and **20** but the third Cl could not be replaced.

$$(CF_3)_2CHOCCl_3 \xrightarrow{} (CF_3)_2CHOCFCl_2 \xrightarrow{} (CF_3)_2CHOCF_2Cl$$
4 **19** **20**

Fluorination of the other ethers **8**, **12**, **13**, and **15** gave similar results, except that **12** could be fluorinated using

$$(CF_3)_2CHOCHCl_2 \xrightarrow{} (CF_3)_2CHOCHFCl \xrightarrow{} (CF_3)_2CHOCHF_2$$
3 **17** **18**

(9) A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Rheinhold Publishing Corp., New York, N. Y., 1958.
(10) M. Hudlicky, "Chemistry of Organic Fluorine Compounds," Macmillan Co., New York, N. Y., 1962.

HF alone and in **13** all three of the chlorines on the $OCCl_3$ group were replaced.

$(CF_2Cl)_2CHOCHCl_2 \longrightarrow (CF_2Cl)_2CHOCHF_2$
8 **21**

$CF_3(CH_3)CHOCHCl_2 \longrightarrow CF_3(CH_3)CHOCHF_2$
12 **22**

$CF_3(CH_3)CClOCHCl_2 \longrightarrow CF_3(CH_3)CFOCHF_2$
15 **23**

$CF_3(CH_3)CHOCCl_3 \longrightarrow CF_3(CH_3)CHOCF_3$
13 **24**

Pharmacology.—Both the liquid and the vapor of all compounds were tested for acidity. All ethers which were stable or neutral were evaluated as anesthetic agents in mice. In general, those ethers having OCH_2Cl, OCHFCl, $OCHCl_2$, or $OCCl_3$ were the least stable, although some could be stabilized sufficiently to permit testing by the addition of K_2CO_3. Seven compounds (**3**, **11**, **12**, **13**, **14**, **15**, **16**) (Table I) could not be stabilized and were too acidic to test.

The anesthetic properties of two isopropyl ethers, **1** and **5** have been reported[11,12] and testing of these compounds was repeated for comparison with the new compounds. Our screening results were in good agreement with those reported. The three fluorinated commercial anesthetics, halothane (**25**), methoxyflurane (**26**), and fluroxene (**27**), are also included in Table I as standard agents for comparison. Most of the fluoroisopropyl ethers showed anesthetic activity, increasing in potency with greater Cl content. Almost all were irritating and some caused convulsions and toxicity indicated by delayed deaths during a 24-hr period following anesthesia.

The good anesthetic properties of **2**, **6**, **7**, **17**, and **18** in mice would indicate further study in other species were it not for the undesirable irritating and toxic side effects, which could be due to dehydrohalogenation.

(11) E. E. Gilbert and B. Veldhuis, U. S. Patent 3,346,448 (to Allied Chemical Corp., New York, N. Y.), Oct 10, 1967; *Chem. Abstr.*, **68**, 12474 (1968).

(12) British Patent 1,141,099 (to Allied Chemical Corp., New York, N. Y.), Jan 22, 1969; *Chem. Abstr.*, **71**, 2970 (1969).

Experimental Section

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

Screening was done using mice, and the agent was administered by inhalation in admixture with oxygen.[13] 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.—Bp were determined by distn or by the Siwoloboff method and are uncorr. The methyl ethers **1**, **5**, **7**, and **10** were prepared by methylation of the appropriate fluoro alcohol as described for **1**.[11] Chlorinations were done using the procedure described by Park.[6,7] The liquid ether was treated with Cl_2 under the illumination of a 250-W incandescent bulb. The progress of the chlorination was followed by titrating the dissolved effluent HCl and the compn of the reaction mixt was determined by glc. Fractional distn or preparative chromatography was used for isolation and purification.

Fluorinations. Method A. $(CF_3)_2CHOCHF_2$ (**18**).—A mixt of 211 g (0.84 mole) of **3**, 150 g (0.84 mole) of anhyd SbF_3, and 5.3 g (2.5% by wt of **3**) of $SbCl_5$ was stirred and heated slowly. The reaction started at 60° at which point the antimony salts darkened and liquefied. The temp dropped to 53° and was held there for 3 hr. The liq prod was distd away from the salts, washed with dil HCl and H_2O, and dried. Fractional distn gave 125 g (0.52 mole) of $(CF_3)_2CHOCHF_2$, bp 41–44.5°, and 20 g (0.085 mole) of $(CF_3)_2CHOCHFCl$, bp 65–67°.

Method B. $(CF_2Cl)_2CHOCHF_2$ (**21**).—Anhyd HF was added slowly *via* a calibrated plastic flowmeter to 99 g (0.35 mole) of **8** and 5 g of $SbCl_5$ (5% by wt of **8**) contd in a 3-necked stainless steel flask fitted with a stirrer, thermometer well, and a copper Dry-Ice condenser. The reaction was run at 0° with ice cooling. The by-product HCl was led from the top of the condenser into a H_2O scrubber and titrated in order to estimate the HF consumed. The HF flow was stopped when the HCl evolution ceased, about 12 min. The prod was washed with cold H_2O and dil HCl and dried over K_2CO_3; 79 g of crude product was purified by vacuum fractionation and 59.5 g (0.24 mole) of $(CF_2Cl)_2CHOCHF_2$, bp 73° (295 mm), was obtained.

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