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NEW INHALATION ANAESTHETICS: II. FLUORINATED METHYL PROPYL ETHERS

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SUMMARY

A range of fluorohalogenated methyl propyl ethers has been prepared for screening as potential inhalation anaesthetics. Many compounds tested were either convulsant or caused marked respiratory depression. Only 2,2,3,3-tetrafluoropropyl methyl ether showed good anaesthesia without side effects, but would also be expected to be flammable at clinical concentrations.

INTRODUCTION

The development of fluorinated ethers as potential inhalation anaesthetics has been widely investigated, and the subject has been reviewed by Larsen[1]. In particular, we have recently reported the synthesis and testing of an extensive range of fluorinated 1,3-dioxolanes [2] and Terrell et al. have published comprehensive data on fluorinated methyl isopropyl ethers [3,4,5,6]. Aliphatic fluoroethers are particularly attractive because of the availability of fluorinated alcohols as starting materials, and also because of recent advances in the fluorination of ethers with high valency metal fluorides[7]. In view of the clinical acceptance of C_4 ethers such as diethyl ether and fluoroxene ($CF_3CH_2OCH{=}CH_2$) we have therefore extended our studies to the synthesis of fluorinated methyl propyl ethers.

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RESULTS AND DISCUSSION

The addition of difluorocarbene to aliphatic alcohols is a convenient route to difluoromethyl ethers[8] but we have found the corresponding reaction with 2,2,3,3-tetrafluoropropanol to be unexpectedly hazardous during the preparation of the sodium alkoxide from sodium metal[9]. The alternative use of potassium hydroxide pellets led to a smooth reaction as shown in figure 1, but the yield of ether was found to depend critically on the absence of water in the starting alcohol. The ether was readily chlorinated as shown, but only the dichloro product was amenable to halogen exchange with antimony trifluoride. Other workers have reported the successful halogen exchange of the monochloro product with bromine trifluoride[10], but we have found that this reaction may also be conveniently effected with cobalt trifluoride as shown.

$$CHF_2CF_2CH_2OH \xrightarrow[KOH]{CHF_2Cl} CHF_2CF_2CH_2OCHF_2$$

$$CHF_2CF_2CH_2OCHF_2 \xrightarrow{Cl_2} CHF_2CF_2CHClOCHF_2 + CHF_2CF_2CCl_2OCHF_2$$

$$CHF_2CF_2CHClOCHF_2 \xrightarrow[155^{o}]{CoF_3} CHF_2CF_2CHFOCHF_2$$

$$CHF_2CF_2CCl_2OCHF_2 \xrightarrow[SbCl_5]{SbF_3} CHF_2CF_2CFClOCHF_2$$

Figure 1

To obtain further compounds in this series, methyl 2,2,3,3-tetrafluoropropyl ether was prepared and exhaustively chlorinated as shown in figure 2. Chlorination was found to proceed readily as far as the tetrachloro product, but became progressively more difficult thereafter. Fluorination of selected chlorinated products with antimony trifluoride afforded a range of further ethers as shown although the exchange of isolated propyl α-chlorine atoms was again observed not to occur with this reagent.

$$CHF_2CF_2CH_2OH + (CH_3)_2SO_4 \xrightarrow{KOH} CHF_2CF_2CH_2OCH_3$$

$$CHF_2CF_2CH_2OCH_3 \xrightarrow{Cl_2} CHF_2CF_2CH_2OCHCl_2 + CHF_2CF_2CH_2OCCl_3$$

cont.

$$+$$

$$CHF_2CF_2CHClOCHCl_2 + CHF_2CF_2CCl_2OCH_2Cl$$

$$+$$

$$CHF_2CF_2CHClOCCl_3 + CF_2ClCF_2CHClOCCl_3$$

$$+$$

$$CF_2ClCF_2CCl_2OCCl_3$$

$$CHF_2CF_2CH_2OCCl_3 \xrightarrow[SbCl_5]{SbF_3} CHF_2CF_2CH_2OCF_2Cl + CHF_2CF_2CH_2OCF_3$$

$$CHF_2CF_2CHClOCCl_3 \xrightarrow[SbCl_5]{SbF_3} CHF_2CF_2CHClOCF_2Cl + CHF_2CF_2CHClOCF_3$$

$$CF_2ClCF_2CHClOCCl_3 \xrightarrow[SbCl_5]{SbF_3} CF_2ClCF_2CHClOCF_2Cl$$

Figure 2

In view of their synthetic potential, we have therefore also studied the preparation of some novel fluoropropanols. Using the England and Melby method[11] for the reaction of sodium cyanide with chlorotrifluoroethylene, we have prepared large quantities of 3-chloro-2,2,3-trifluoropropionic acid, esterified the acid and reduced it to the corresponding chlorotrifluoropropanol as shown in figure 3. Methylation gave the desired methyl propyl ether, which was fluorinated readily with cobalt trifluoride as also shown.

$$CHFClCF_2COOC_2H_5 \xrightarrow{NaBH_4} CHFClCF_2CH_2OH \xrightarrow{(CH_3)_2SO_4} CHFClCF_2CH_2OCH_3$$

$$CHFClCF_2CH_2OCH_3 \xrightarrow[110-140^{o}]{CoF_3} CF_2ClCF_2CF_2OCH_2F + CF_2ClCF_2CH_2OCHF_2$$

$$+$$

$$CF_2ClCF_2CHFOCHF_2 + CHFClCF_2CHFOCHF_2$$

Figure 3

Interestingly, although chlorine migration is a feature of fluorinations with high valency metal fluorides [12] we have found no evidence of such a phenomenon in this case. The reason for this is not clear.

The England and Melby procedure is not generally convenient for fluoroolefin additions because of the requirement for an autoclave, but Troilo and Gambaretto[13] have published an elegant alternative which generates the olefin (presumed) in situ and may be carried out at atmospheric pressure, as shown in figure 4. We have found this reaction to be a particularly convenient and simple route to the propionate ester, which we have also reduced and methylated as shown.

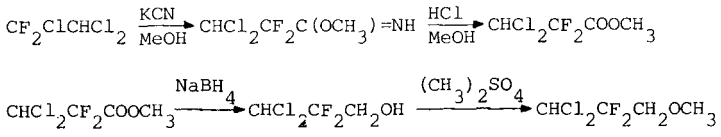

Figure 4

We have now extended the Troilo and Gambaretto procedure to the synthesis of methyl 3-bromo-2,2,3-trifluoropropionate, from which by a similar reaction sequence we have also prepared the corresponding methyl propyl ether as shown in figure 5.

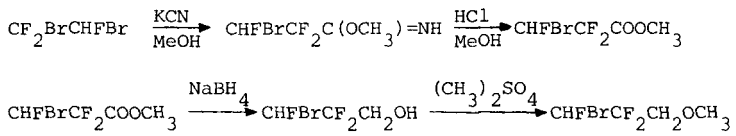

Figure 5

BIOLOGICAL ACTIVITY

Anaesthetic tests were performed on mice in an oxygen atmosphere to determine a minimum anaesthetic concentration which would just produce anaesthesia in thirty minutes in individual mice. A minimum lethal concentration which would just produce death in thirty minutes was also obtained, and the results are shown in table 1.

Many ethers induced either convulsions or marked respiratory depression, with or without some degree of anaesthesia. Only 2,2,3,3-tetrafluoropropyl methyl ether gave good anaesthesia without side effects, but the compound could be inflammable at clinical concentrations[1].

TABLE 1

Physical and Biological Data of Some Fluorinated Methyl Propyl Ethers

All compounds are new unless marked *

Compound	b.p. °C	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
*$CHF_2CF_2CH_2OCHF_2$	69	1.4	>2.2	convulsant
*$CHF_2CF_2CHClOCHF_2$	94-5	0.2	1.3	marked respiratory depression
*$CHF_2CF_2CCl_2OCHF_2$	>100	0.5	1.6	convulsant
$CHF_2CF_2CH_2OCH_3$	64-8	2.3	7.8	good anaesthesia
$CHF_2CF_2CH_2OCHCl_2$	130	0.6	1.0	severe lung damage
$CHF_2CF_2CH_2OCCl_3$	145	25-50mg/kg	100-150mg/kg	convulsant
$CHF_2CF_2CHClOCHCl_2$	150	25-50mg/kg	250-300mg/kg	excitable
$CHF_2CF_2CCl_2OCH_2Cl$				not tested
$CHF_2CF_2CHClOCCl_3$	155	100mg/kg	350-400mg/kg	convulsant
$CF_2ClCF_2CHClOCCl_3$				not tested
$CF_2ClCF_2CCl_2OCCl_3$				not tested
$CHF_2CF_2CH_2OCF_2Cl$	<70	Tested @ 0.1-0.6		severe convulsant at all concns.
$CHF_2CF_2CH_2OCF_3$	<70	25-50mg/kg	250-300mg/kg	severe convulsant at all concns.

TABLE 1 (cont)

Compound	b.p. °C	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
$CHF_2CF_2CHClOCF_2Cl$	ca. 70	0.5	>1.4	convulsant
$CHF_2CF_2CHClOCF_3$	<70	1.77	3.3	marked respiratory depression
*$CHF_2CF_2CHFOCHF_2$	74	0.5	2.0	marked respiratory depression
*$CHF_2CF_2CFClOCHF_2$	77	<3.1	-	convulsant at 1.2% and 3.1%
$CF_2ClCF_2CHClOCF_2Cl$	106.5	200-250mg/kg	350-400mg/kg	convulsant
$CHCl_2CF_2COOCH_3$	152	200-250mg/kg	>400mg/kg	irritant
$CHCl_2CF_2CH_2OH$	161	100-120mg/kg	>200mg/kg	no analgesia
$CHCl_2CF_2CH_2OCH_3$	139	100-150mg/kg	300-350mg/kg	very slow
$CHFClCF_2CH_2OCH_3$	104			not tested
$CF_2ClCF_2CF_2OCH_2F$				not tested
$CF_2ClCF_2CH_2OCHF_2$				not tested
$CF_2ClCF_2CHFOCHF_2$	76	0.8	3.3	marked respiratory depression
$CHFClCF_2CHFOCHF_2$	100	0.4	1.1	marked respiratory depression
$CHFBrCF_2C(OCH_3)=NH$	129	150-200mg/kg	>400mg/kg	no true anaesthesia

TABLE 1 (cont)

Compound	b.p. °C	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
$CHFBrCF_2COOCH_3$	139	400mg/kg	>400mg/kg	not relaxed
$CHFBrCF_2CH_2OH$	149	100-150mg/kg	>400mg/kg	poor analgesia
$CHFBrCF_2CH_2OCH_3$	125	0.8	1.5	very slow

a. v/v% in oxygen, or mg/kg body weight for i.v. administration. (-) signifies no reliable estimate obtained.

EXPERIMENTAL

Materials and Methods

Fluorinated reagents were obtained from Fluorochem Ltd., Glossop, England. Boiling points were determined by the Siwoloboff method in a Buchi capillary melting point apparatus and are uncorrected. Gas chromatography was performed on a Pye 104 analytical chromatograph and a Varian Autoprep preparative chromatograph, using either 15% silicone gum (SE 30), 15% diethyl hexyl sebacate (DEHS) or 20% carbowax on chromosorb W.

^{1}H nmr spectra were recorded on Perkin Elmer R12/Varian A60 spectrometers at 60 MHz, or on Varian HA 100/Varian HA 100D spectrometers at 100 MHz. Mass spectra were recorded on an AEI MS9 spectrometer or a Perkin Elmer Hitachi spectrometer. Infra-red spectra were recorded on a Perkin Elmer 157 instrument and were used for comparative identification with authenticated compounds.

Preparation of 2,2,3,3-tetrafluoropropyl difluoromethyl ether

Chlorodifluoromethane (10 l/hr) was bubbled for 5 hr through a solution of anhydrous potassium hydroxide (84g) in 2,2,3,3-tetrafluoropropan-1-ol (350g) at 45° under reflux. Fractional distillation gave 2,2,3,3-tetrafluoropropyl difluoromethyl ether (48.7g) b.p. 69° [Found: C,26.5; H,2.2%; M(Mass Spec) 163. $C_4H_4F_6O$ requires C,26.4; H,2.2%; M-F (Mass Spec)163] ^{1}H nmr 4.19δ (2H,t,$-CH_2O-$, $^{3}J_{CH_2CF_2}$ 12.5Hz), 5.88δ(1H,tt, CHF_2CF_2-, $^{2}J_{HF}$ 53Hz), 6.25δ(1H,t,CHF_2O-, $^{2}J_{HF}$ 73Hz).

Chlorination of 2,2,3,3-tetrafluoropropyl difluoromethyl ether

The ether (60g) was chlorinated as previously described [2] to give a product (66.6g) which was fractionated as shown (from 34g Cl_2).

fraction	boiling range	wt	g.l.c.(SE 30,65°)
A	81-90°	23.6g	I
B	90-95°	31.8g	mainly II
C	residue	6.9g	II + III

Fraction A was shown by i.r. spectroscopy to be starting material. A portion of fraction B was purified by g.l.c. to give (II) 1-chloro-2,2,3,3-tetrafluoropropyl difluoromethyl ether b.p. 94-5° [Found:

C,19.5; H, 0.8%; M(Mass Spec)181.$C_4H_3ClF_6O$ requires C, 19.1; H, 0.78%; M-Cl(Mass Spec)181 ^{1}H nmr 6.09δ(1H, m, CHF_2CF_2-), 6.12δ(1H, m, -CHCl-), 6.49δ(1H, m, CHF_2O-). Fraction C was separated by g.l.c. to give a further sample of II (2.2g) and (III) 1,1-dichloro-2,2,3,3-tetrafluoropropyl difluoromethyl ether (1.0g) b.p. >100° [Found: C,22.4; H,1.3; Cl,16.3%; M(Mass Spec)215. $C_4H_2Cl_2F_6O$ requires C,22.2; H,1.4; Cl,16.4%; M-Cl(Mass Spec)215] ^{1}H nmr 6.19δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 52Hz), 6.90δ(1H, t, CHF_2O-, $^2J_{HF}$ 68Hz).

Preparation of 2,2,3,3-tetrafluoropropyl methyl ether

2,2,3,3-tetrafluoropropan-1-ol (132g) was introduced slowly into a stirred solution of potassium hydroxide (86g) in water (100cm^3). Dimethyl sulphate (164g) was added dropwise, and the reaction mixture was stirred at ambient temperature for 12hr. Fractionation gave a single fraction (135g) b.p. 64-68°, which was washed with water (25cm^3) and the organic layer dried to give 2,2,3,3-tetrafluoropropyl methyl ether (121.5g) b.p. 64-8° [Found: C,33.2; H,4.3%; M(Mass Spec)146. $C_4H_6F_4O$ requires C,32.9; H,4.1%; M(Mass Spec)146] ^{1}H nmr 3.48δ (3H, s, CH_3O-) 3.75δ(2H, t,-CH_2O-, $^3J_{CH_2CF_2}$ 12.0Hz), 5.88δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.5Hz).

Chlorination of 2,2,3,3-tetrafluoropropyl methyl ether

The ether (69.7g) was chlorinated (8.5g Cl_2) to give a product (100g) shown by g.l.c. (SE30, 95°) to contain four major compounds. Separation of a small portion by g.l.c. gave (i) 2,2,3,3-tetrafluoropropyl dichloromethyl ether b.p. 130° [Found: C,22.8; H,1.9; Cl,33.2%; M(Mass Spec)213. $C_4H_4Cl_2F_4O$ requires C,22.4; H,1.9; Cl,33.0%; M-H(Mass Spec)213] ^{1}H nmr 4.21δ(2H, t, -CH_2O-, $^3J_{CH_2CF_2}$ 11.0Hz), 5.72δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 49.5Hz), 7.20δ(1H, s, $CHCl_2O$-), (ii) 2,2,3,3-tetrafluoropropyl trichloromethyl ether (trace) b.p. 145° [Found: C,19.3; H,1.4%; M(Mass Spec)247. $C_4H_3Cl_3F_4O$ requires C,19.2- H,1.2%; M-H(Mass Spec)247] ^{1}H nmr 4.45δ(2H, t, -CH_2O-, $^3J_{CH_2CF_2}$ 15.5Hz), 5.94δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.5Hz), (iii) 1-chloro-2,2,3,3-tetrafluoropropyl dichloromethyl ether b.p. 150° [Found: C,19.5; H,1.2; Cl,41.6%, M(Mass Spec)247. $C_4H_3Cl_3F_4O$ requires C,19.2; H,1.2; Cl,42.8%; M-H(Mass Spec)247] ^{1}H nmr 6.02δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.5Hz), 6.04δ(1H, t, -CHClO-, $^3J_{CHCF_2}$ 8.0Hz), 7.19δ(1H, s, $CHCl_2O$-), and (iv) 1,1-dichloro-2,2,3,2-tetrafluoropropyl chloromethyl ether (trace) [Found: M(Mass Spec)247. $C_4H_3Cl_3F_4O$ requires M-H(Mass Spec)247] ^{1}H nmr 5.72δ(2H, s, CH_2ClO-), 6.08δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.0Hz).

A portion (16g) of the product mixture was added to further starting material (47g) and chlorinated (85g Cl_2) to give a new product mixture (93.2g) which was fractionally distilled.

fraction	boiling range	wt.	g.l.c. (SE30, 95°)
A	135-149°	22.6g	I + II
B	150-157°	22.9g	I + II + III
C	residue	42.3g	Mainly III

I and II were identified as 2,2,3,3-tetrafluoropropyl trichloromethyl ether and 1-chloro-2,2,3,3-tetrafluoropropyl dichloromethyl ether from g.l.c. retention times. A small portion of the residue was purified by g.l.c. to give 1-chloro-2,2,3,3-tetrafluoropropyl trichloromethyl ether b.p. 155° [Found: C,16.9; H,0.9; Cl,49.7%; M(Mass Spec) 247. $C_4H_2Cl_4F_4O$ requires C,16.9; H,0.7; Cl,50.0%; M-Cl(Mass Spec)247] ^{1}H nmr 6.10δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.5Hz), 6.30δ(1H, t, -CHClO-, $^3J_{CHCF_2}$ 8.0Hz).

Fraction B and the remainder of the residue (total 60g) were further chlorinated (12l/hr Cl_2) without water cooling for 14hr. Fractionation of the product (40g) gave

fraction	boiling range°C	weight
D	55-77	7.9g
E	78-80	5.1g
F	100-160	5.3g
G	160-175	8.8g
H	175—	8.7g
residue		0.6g

Fractions D and E were identified as carbon tetrachloride by i.r. spectroscopy. A portion (500μl) of fraction H was separated by g.l.c. (SE30, 130°) to give (i) 1,3-dichloro-2,2,3,3-tetrafluoropropyl trichloromethyl ether (370mg) [Found: C,15.2; H,0.5: Cl,53.8%; M(Mass Spec)281. $C_4HCl_5F_4O$ requires C,15.1; H,0.3; Cl,55.7%; M-Cl(Mass Spec)281] ^{1}H nmr 6.46δ (1H, m, -CHClO-) and (ii) 1,1,3-trichlorotetrafluoropropyl trichloromethyl ether (170mg) [Found: C,13.6; H,0.0; Cl,60.0%; M(Mass Spec)217. $C_4Cl_6F_4O$ requires C,13.6; H,0.0; Cl,60.4%; M-$OCCl_3$(Mass Spec)217] ^{1}H nmr no signal.

Fluorination of 2,2,3,3-tetrafluoropropyl trichloromethyl ether

The ether (22.4g) was added dropwise to a stirred mixture of antimony trifluoride (20.0g) and antimony pentachloride (0.4cm^3), and the product (13.6g, b.p. 60-68°) allowed to distil as it formed. The two major com-

ponents were separated by g.l.c. (SE30) to give (i) 2,2,3,3-tetrafluoropropyl chlorodifluoromethyl ether b.p. <70° [Found: C,22.3; H,1.4; Cl,16.1%. $C_4H_3ClF_6O$ requires C,22.2; H,1.4; Cl,16.4%] ^{1}H nmr 4.35δ(2H, t, $-CH_2O-$, $^3J_{CH_2CF_2}$ 10.5Hz), 5.92δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.4Hz) and (ii) 2,2,3,3-tetrafluoropropyl trifluoromethyl ether b.p. <70° [Found: C,23.9; H,1.7%; M(Mass Spec)200. $C_4H_3F_7O$ requires C,23.9; H,1.7%; M(Mass Spec)200] ^{1}H nmr 4.32δ(2H, t,$-CH_2O-$, $^3J_{CH_2CF_2}$ 12.0Hz), 5.92δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.0Hz).

Fluorination of 1-chloro-2,2,3,3-tetrafluoropropyl trichloromethyl ether

The ether (55g) was fluorinated with antimony trifluoride (55g) and antimony pentachloride (2cm^3) at 100-120°, and the product (36.3g, b.p. 63-70°) allowed to distil as it formed. The product mixture was washed with water (25cm^3) and the organic layer dried ($MgSO_4$) to give a clear liquid (17.6g), a portion (5.75cm^3) of which was separated by g.l.c. (carbowax 75°) to give (i) 1-chloro-2,2,3,3-tetrafluoropropyl chlorodifluoromethyl ether (2.2g) b.p. ∿70° [Found: C,19.2; H,1.0; Cl,27.6%; M(Mass Spec)215. $C_4H_2Cl_2F_6O$ requires C,19.1; H,0.8; Cl,28.3%; M-Cl(Mass Spec)215] ^{1}H nmr 6.10δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.5Hz), 6.20δ(1H, t, $-CHClO-$, $^3J_{CHClCF_2}$ 8.0Hz), (ii) 1-chloro-2,2,3,3-tetrafluoropropyl trifluoromethyl ether (2.6g) b.p. <70° [Found: C,20.3; H,1.2; Cl,14.6%, M(Mass Spec)199. $C_4H_2ClF_7O$ requires C,20.5; H,0.9; Cl,15.1%; M-Cl(Mass Spec)199] ^{1}H nmr 6.08δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 53.5Hz), 6.19δ(1H, t $-CHClO-$, $^3J_{CHClCF_2}$ 6.6Hz), and (iii) an unidentified mixture (0.6g).

Fluorination of 1-chloro-2,2,3,3-tetrafluoropropyl difluoromethyl ether

The ether (18g) was added dropwise to stirred cobalt trifluoride (100g) at 155° in PTFE-sprayed glassware, and the product (4.1g, boiling range 60-130°) allowed to distil as it formed. The product was purified by g.l.c. (SE30) to give 1,2,2,3,3-pentafluoropropyl difluoromethyl ether b.p. 74° [Found: C,24.3; H,1.6%; M(Mass Spec)181. $C_4H_3F_7O$ requires C,24.0; H,1.5%; M-F(Mass Spec)181] ^{1}H nmr 5.95δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 52.0Hz), 5.98δ(1H, dt, $-CHFO-$, $^2J_{HF}$ 55.0Hz), 6.46δ(1H, t, CHF_2O-, $^2J_{HF}$ 72.0Hz).

Fluorination of 1,1-dichloro-2,2,3,3-tetrafluoropropyl difluoromethyl ether

The ether (11.2g) was fluorinated with antimony trifluoride (15g) and antimony pentachloride (0.5cm^3). Distillation gave a product (3.6g) which

was separated by g.l.c. (SE30,50°) to give two unstable, fuming components and 1-chloro-1,2,2,3,3-pentafluoropropyl difluoromethyl ether (860mg) b.p. 77° [Found: C,20.5; H,0.7; Cl,15.1%; M(Mass Spec)199. $C_4H_2ClF_7O$ requires C,20.4; H,0.9; Cl,15.1%; M-Cl(Mass Spec)199] ^{1}H nmr 6.08δ(1H, tt, CHF_2CF_2-, $^2J_{HF}$ 49.5Hz), 6.81δ(1H, t, CHF_2O-, $^2J_{HF}$ 61.0Hz).

Fluorination of 1,3-dichloro-2,2,3,3-tetrafluoropropyl trichloromethyl ether

The ether(16.3g) was fluorinated with antimony trifluoride (25g) and antimony pentachloride (0.5cm^3). Distillation gave a product (9.8g) boiling range 90-100°, a portion (750μl) of which was separated by g.l.c. (SE30,75°) to give (i) 1,3-dichloro-2,2,3,3-tetrafluoropropyl chlorodifluoromethyl ether (460mg) b.p. 106.5° [Found: C,16.9; H,0.3; Cl,38.1%; M (Mass Spec)283. $C_4HCl_3F_6O$ requires C,16.8; H,0.4; Cl,37.4%; M-H(Mass Spec) 283] ^{1}H nmr 6.40δ(1H, m, -CHClO-) and (ii) 1,1,1,3-tetrachlorotetrafluoropropane, identified by i.r. comparison with an authentic sample.

Preparation of 3,3-dichloro-2,2-difluoropropyl methyl ether

1,1-difluoro-1,2,2-trichloroethane (678g) was added dropwise to a stirred solution of methanol (800cm^3) and potassium cyanide (400g) in water (300cm^3), and the reaction mixture allowed to stand for 12hr. The reaction mixture was heatedto 55° for 4hr, cooled to ambient temperature, diluted with water (8L) and stirred rapidly for 30 min. The organic layer was separated and dried ($MgSO_4$) to give 3,3-dichloro-2,2-difluoro-1-iminopropyl methyl ether (606g), mixed with methanol (500cm^3) and treated with anhydrous hydrogen chloride for 1hr at ambient temperature, and for 3hr at 73°. The reaction mixture was diluted with water (2L), the organic layer separated and dried ($MgSO_4$), and a small portion of the product (542g) purified by distillation to give methyl 3,3-dichloro-2,2-difluoropropionate b.p. 152° [Found: C,25.7; H,2.1; Cl,33.4%; M(Mass Spec)172. $C_4H_4Cl_2F_2O_2$ requires C, 25.0; H,2.1; Cl,36.8%; M-HF(Mass Spec)172] ^{1}H nmr 3.96δ(3H, s, CH_3-), 6.08δ (1H, t, $CHCl_2$-, $^3J_{CHCF_2}$ 11.5Hz). The ester (498.5g) in methanol (3.25L) was treated slowly with $NaBH_4$ (195g), the reaction mixture being stirred for 12hr, acidified and filtered. The product was isolated by fractional distillation, extracted with ether, and the extracts dried ($MgSO_4$). Fractionation gave a single fraction (318g) boiling range 163-182°, which was shaken with saturated sodium bicarbonate solution and dried ($MgSO_4$) to give one product (300g), a small portion of which was purified by g.l.c. (SE30,140°) and identified as 3,3-dichloro-2,2-difluoropropan-1-ol b.p. 161° [Found: C,22.2; H,2.7; Cl,42.3%; M(Mass Spec)144. $C_3H_4Cl_2F_2O$

requires C,21.8; H,2.4; Cl,43.0%; M-HF(Mass Spec)144] ^{1}H nmr 3.00δ(1H, s, -OH), 4.08δ(2H, t, $-CH_2O-$, $^{3}J_{CH_2CF_2}$ 12.0Hz), 5.99δ(1H, t, $CHCl_2$, $^{3}J_{CH_2CF_2}$ 8.0Hz). The alcohol (21g) was treated with dimethyl sulphate (31.6g) and potassium hydroxide (12g) in water (120cm^3) as previously described to give 3,3-dichloro-2,2-difluoropropyl methyl ether (25g) b.p. 139° [Found: C,26.5; H,3.5; Cl,37.9%. $C_4H_6Cl_2F_2O$ requires C,26.8; H,3.4; Cl,39.6%] ^{1}H nmr 3.52δ (3H, s, CH_3O-), 3.88δ(2H, t, $-CH_2O-$, J_{CHCF_2} 10.5Hz), 5.92δ(1H, t, $CHCl_2-$, J_{CHCF_2} 8.5Hz).

Preparation of 3-bromo-2,2,3-trifluoropropyl methyl ether

In a similar manner to that described above, 1,2-dibromo-1,2,2-trifluoroethane (140g) was treated with potassium cyanide (72g) and methanol (150cm^3) in water (75cm^3) to give 3-bromo-2,2,3-trifluoro-1-iminopropyl methyl ether (93g) b.p. 129° [Found: C,21.9; H,2.6; N,6.8; Br,36.3%; M(Mass Spec)219. $C_4H_5BrF_3ON$ requires C,21.8; H,2.3; N,6.4; Br,36.3%; M(Mass Spec) 219] ^{1}H nmr 3.88δ(3H, s, CH_3-), 6.58δ(1H, dt, CHFBr-, $^{2}J_{HF}$ 45.5Hz), 8.0δ (1H, NH). The iminoether (85g) was treated with methanol (120cm^3) and hydrogen chloride gas for 5hr to give methyl 3-bromo-2,2,3-trifluoropropionate (70g) b.p. 139° [Found: C,21.9; H,1.9%; M(Mass Spec)220. $C_4H_4F_3BrO_2$ requires C,21.8; H,1.8%; M(Mass Spec)220] ^{1}H nmr 4.02δ(3H, s, CH_3-), 6.75δ (1H, dt, CHFBr-, $^{2}J_{HF}$ 47.5Hz). The ester (65g) was reduced with $NaBH_4$ (22.7g) to give 3-bromo-2,2,3-trifluoropropan-1-ol (35g) b.p. 149° [Found: C,19.0; H,2.2%; M(Mass Spec)192. $C_3H_4F_3BrO$ requires C,18.6; H,2.1%; M(Mass Spec)192] ^{1}H nmr 4.05δ(2H, t, $-CH_2O-$ $^{3}J_{CH_2CF_2}$ 12.0Hz),6.60δ(1H,dt,CHFBr-,$^{2}J_{HF}$ 48.0Hz). The alcohol (5g) was treated with dimethyl sulphate (6.55g) and sodium hydroxide (2.4g) in water (24cm^3) to give 3-bromo-2,2,3-trifluoropropyl methyl ether (3.5g) b.p. 125° [Found: C,23.2; H,3.0% M(Mass Spec) 206. $C_4H_6F_3BrO$ requires C,23.2; H,2.9%; M(Mass Spec)206] ^{1}H nmr 3.50δ(3H, s, CH_3O-), 3.80δ(2H, t, $-CH_2O-$, $^{3}J_{CH_2CF_2}$ 12.0Hz), 6.56δ(1H, dt, CHFBr-, $^{2}J_{HF}$ 47.5Hz).

Preparation of 3-chloro-2,2,3-trifluoropropyl methyl ether

In a similar manner to that described above, ethyl 3-chloro-2,2,3-trifluoropropionate (prepared from 3-chloro-2,2,3-trifluoropropionic acid) was reduced and methylated to give 3-chloro-2,2,3-trifluoropropyl methyl ether b.p. 104° [Found: C,30.2; H,3.8; Cl,20.0%. $C_4H_6ClF_3O$ requires C,29.6; H, 3.7; Cl,21.3%] ^{1}H nmr 3.48δ(3H, s, CH_3O-), 3.78δ(2H, t, $-CH_2O-$, $^{3}J_{CH_2CF_2}$ 12.0Hz), 6.30δ(1H, dt, CHFCl-, $^{2}J_{HF}$ 48.0Hz).

Fluorination of 3-chloro-2,2,3-trifluoropropyl methyl ether

The ether (20g) was fluorinated at 110-140° in a conventional CoF_3 reactor to give a product (12.8g) which was fractionally distilled:-

fraction no.	boiling range °C	wt.
1	30-36	0.75g
2	57-62	2.75g
3	64	2.20g
4	64-70	1.05g
5	74	0.90g

Fraction 2 was separated by g.l.c. (DEHS, 55°) to give (i) 3-chloro-hexafluoropropyl fluoromethyl ether (75mg) ^{1}H nmr 5.62δ (d, CH_2FO-, $^2J_{HF}$ 51.0Hz), (ii) 3-chloro-2,2,3,3-tetrafluoropropyl difluoromethyl ether (150mg) ^{1}H nmr 4.30δ (2H, t, $-CH_2O-$, $^3J_{CH_2CF_2}$ 13.0Hz) and (iii) 3-chloro-1,2,2,3,3-pentafluoropropyl difluoromethyl ether (1.85g) b.p. 76° Found: M(Mass Spec) 215. $C_4H_2ClF_7O$ requires M-F(Mass Spec) 215 ^{1}H nmr 6.10δ (dt, CHFO-, $^2J_{HF}$ 54.5Hz), 6.45δ (t, CHF_2O-, $^2J_{HF}$ 71.0Hz). Fraction 5 was separated by g.l.c. (DEHS, 85°) to give 3-chloro-1,2,2,3-tetrafluoropropyl difluoromethyl ether (0.5g) b.p. 100° [Found: C,22.5; H,1.6%; M(Mass Spec) 181. $C_4H_3ClF_6O$ requires C,22.2; H,1.4%; M-Cl(Mass Spec) 181] ^{1}H nmr 6.06δ (1H, dt, -CHFO-, $^2J_{HF}$ 56.0Hz), 6.32δ (1H, dt, CHFCl-, $^2J_{HF}$ 48.0Hz), 6.47δ (1H, t, CHF_2O-, $^2J_{HF}$ 70.5Hz).

Anaesthetic Test

Ideal gas laws and liquid density were used to calculate the volume of any liquid required to give a standard gas concentration when volatilised in a 500cm^3 flask of oxygen. A range of such concentrations for each compound was made up and tested with individual mice to find a minimum anaesthetic concentration which would just give anaesthesia after 30 min. exposure. A minimum lethal concentration was similarly estimated. Some of the less volatile compounds, however, were tested intravenously as emulsions in 'Cremophor', in which case anaesthesia was assessed at 2 min., and the results expressed in mg/kg body weight. Further details on the biological tests will be published elsewhere [14].

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