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NEW INHALATION ANAESTHETICS: IV. FLUORINATED PROPANES

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SUMMARY

A range of fluorohalopropanes has been synthesised for screening as potential inhalation anaesthetics. Of the 26 compounds tested 21 are novel, and a further 6 novel propanes are also described. Of the compounds screened, 14 gave good anaesthesia with minimal side effects in mice, and their biological activities will be described more fully elsewhere *[1]*.

INTRODUCTION

Previous papers in this series have described the syntheses of fluorohalogenated 1,3-dioxolanes *[2]*, methyl propyl ethers *[3]*, methyl ethyl ethers *[4]*, diethyl ethers *[4]* and methyl butyl ethers *[4]* as potential inhalation anaesthetics. However, the leading inhalation anaesthetic, 'Fluothane'* ($CF_3CHBrCl$) - Imperial Chemical Industries Ltd., is an alkane, and we have therefore now extended our studies to include volatile fluorohalogenated simple alkanes. In this paper we describe the preparation and biological testing of some novel fluorohalogenated propanes.

RESULTS AND DISCUSSION

The consumption of a volatile anaesthetic agent is routinely conserved by returning any exhaled vapours to the patient through a soda-

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*Trade mark the property of Imperial Chemical Industries Ltd.

lime cannister to remove unwanted carbon dioxide. Simultaneous removal of water vapour is also exothermic, and it is therefore a necessary requirement of any novel inhalation anaesthetic that it be stable under these conditions. Since the expected reaction with halogenated hydrocarbons is dehydrohalogenation, and since dehydrofluorination is generally regarded as the most difficult of these, we have concentrated our efforts on the synthesis of novel 2,2-difluorinated propanes as a continuation of previous unpublished work by ICI Ltd. Novel compounds have been underlined for clarity.

Vapour phase bromination of 1,1,2,2,3-pentafluoropropane gave two novel propanes, as shown in figure 1.

$$CHF_2CF_2CH_2F \xrightarrow[400\text{-}480^{o}]{Br_2} CHF_2CF_2CHFBr + \underline{CHF_2CF_2CFBr_2}$$

$$+ CF_2BrCF_2CHFBr + \underline{CF_2BrCF_2CFBr_2}$$

$$+ CF_2BrCFBr_2$$

Figure 1

Considerable pyrolysis was observed, and could account for the presence of a brominated ethane in the product mixture.

Simple chlorination and bromination of the readily prepared 1-chloro-1,2,2,3-tetrafluoropropane afforded all possible products, including seven novel propanes as shown in figure 2.

$$CHFClCF_2CH_2F \xrightarrow[uv]{Cl_2} \underline{CFCl_2CF_2CH_2F} + \underline{CHFClCF_2CHFCl}$$

$$+ CFCl_2CF_2CHFCl + CFCl_2CF_2CFCl_2$$

$$\xrightarrow[440^{o}]{Br_2} \underline{CFBrClCF_2CH_2F} + \underline{CHFClCF_2CHFBr}$$

$$+ \underline{CFBrClCF_2CHFBr} + \underline{CHFClCF_2CFBr_2}$$

$$+ \underline{CFBrClCF_2CFBr_2}$$

Figure 2

The starting propane in figure 2 was prepared by reaction of the tosyl ester of 3-chloro-2,2,3-trifluoropropan-1-ol *[3]* with potassium fluoride. A similar reaction with the tosyl ester of 3-bromo-2,2,3-trifluoropropan-1-ol *[3]* was also successful, but was surprisingly accompanied by the formation of small amounts of the corresponding chloro- and bromoderivatives as shown in figure 3. Unexpectedly, the equivalent reaction with the tosyl ester of 3,3- dichloro-2,2-difluoro-propan-1-ol *[3]* resulted in dehydrofluorination to give as the major product the propene shown in figure 3.

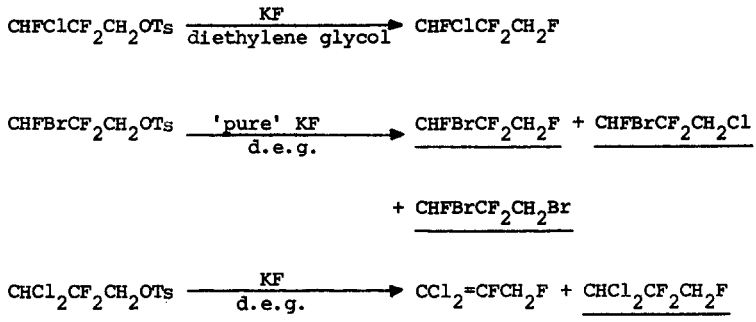

Figure 3

A particularly useful starting material for the preparation of novel propanes is 2-chloroallyl fluoride, itself readily prepared by the action of potassium fluoride on the commercially available 2-chloroallyl chloride. We have prepared both the bromo- and chloroadducts, and have fluorinated these further in standard laboratory glassware using antimony dichloridetrifluoride, as summarised in figure 4. Interestly, two of the products, $CH_2BrCF_2CH_2Br$ and $CH_2ClCF_2CH_2Cl$, might have arisen by rearrangement. It is known from elsewhere *[5,6]* that such rearrangements are possible in the presence of Lewis acids such as aluminium trichloride, and we would suggest that antimony halides may also be able to effect this process.

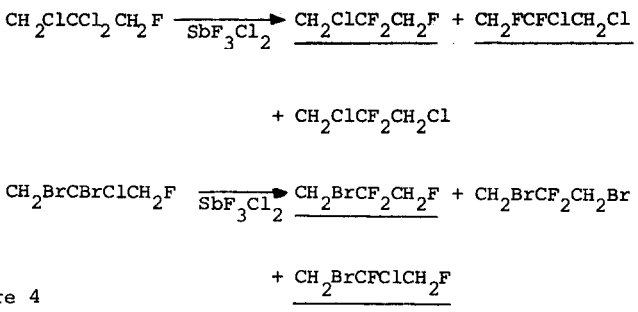

Figure 4

Many of the novel halogenated propanes which might be considered as potential inhalation anaesthetics contain bromine, and several such compounds were synthesised from methylacetylene by the reaction sequences outlined in figure 5. It was found necessary to activate antimony trifluoride by the addition of both antimony pentachloride and bromine to effect halogen exchange, and to obtain the most highly fluorinated products it was necessary to use antimony pentafluoride. Not surprisingly some interchange of chlorine and bromine was also observed with the former reagents. All reactions were, however, conveniently carried out in standard laboratory glassware.

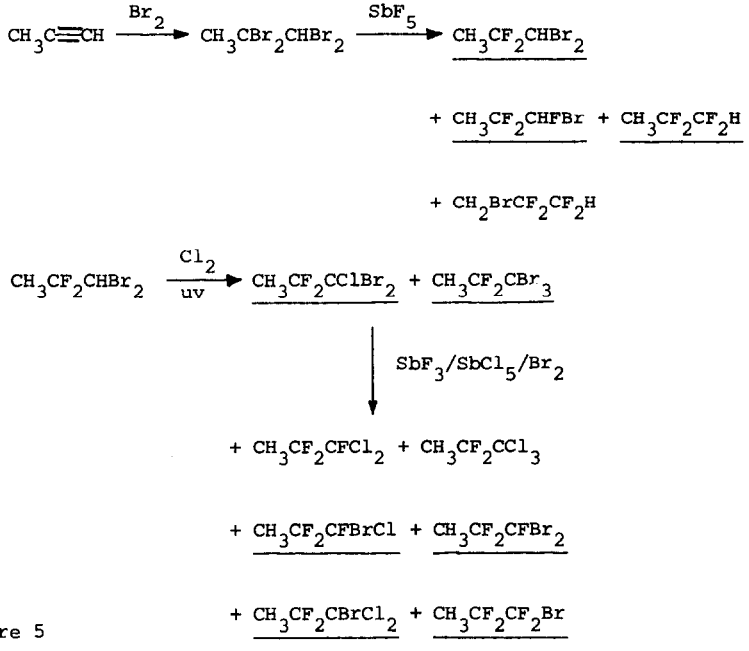

Figure 5

Finally, two simple reactions were carried out to obtain specific propanes which were known to be novel, and which it was hoped might have useful anaesthetic properties. These are shown in figure 6.

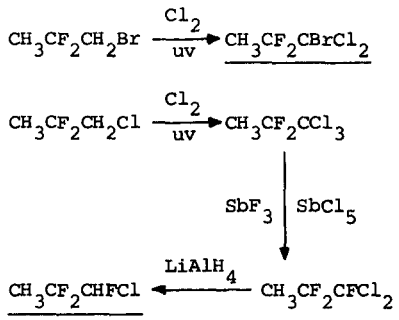

Figure 6

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.

Fourteen propanes gave good anaesthesia with minimal side effects, and their biological activities will be described more fully elsewhere*[1]*.

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 carried out as previously described *[4]* using either silicone gum (SE 30), diethyl hexyl sebacate (DEHS) or carbowax on chromosorb W. All spectra were obtained as previously described *[4]*.

TABLE 1

Anaesthetic Properties of Fluorinated Propanes

*novel compound

Compound	bp °C	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
$CHF_2CF_2CH_2F$		10.0	24.0	minimal side effects
CF_2BrCF_2CHFBr	98			not tested
(nc)*$CHF_2CF_2CFBr_2$		0.3	1.2-1.6	minimal side effects
(nc)*$CF_2BrCF_2CFBr_2$				not tested
CHF_2CF_2CHFBr				not tested
(nc)*$CFCl_2CF_2CH_2F$	73	1.0	4.0	minimal side effects
(nc)*$CHFClCF_2CHFCl$	70	0.5	>1.5	rolling convulsions
$CFCl_2CF_2CHFCl$	96.5			not tested
$CFCl_2CF_2CFCl_2$	116.5			not tested
(nc)*$CFBrClCF_2CH_2F$	94	~0.7	~2.7	minimal side effects
(nc)*$CHFClCF_2CHFBr$		0.4	-	minimal side effects
(nc)*$CFBrClCF_2CHFBr$	137			not tested
(nc)*$CHFClCF_2CFBr_2$	137			not tested

TABLE 1 (cont.)

	Compound	bp °C	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
(nc)	*$CFBrClCF_2CFBr_2$				not tested
	$CCl_2=CFCH_2F$	92	∿ 0.6	-	delayed death at all conc$^{ns.}$
(nc)	*$CHCl_2CF_2CH_2F$	90	0.4-0.6	2.8-3.1	minimal side effects
(nc)	*$CHFBrCF_2CH_2F$	75	0.9-1.1	3.9-4.3	minimal side effects
(nc)	*$CHFBrCF_2CH_2Cl$	110	0.2-0.4	∿1.2	respiratory depression
(nc)	*$CHFBrCF_2CH_2Br$	129	0.2	∿0.7	marked respiratory depression
(nc)	*$CH_2ClCF_2CH_2F$	∿60	1.3-2.0	∿4.3	tremors and lung damage at 4.3%
(nc)	*$CH_2FCFClCH_2Cl$	94.5	<0.9	∿3.5	hiccup respiration
	$CH_2ClCF_2CH_2Cl$	66			not tested
(nc)	*$CH_2BrCF_2CH_2F$	79-80	0.8-1.3	∿4.0	minimal side effects
	$CH_2BrCF_2CH_2Br$	139	0.3	1.0	minimal side effects
	$CH_3CF_2CCl_3$	100	0.6-1.2	3.0	no analgesia
	$CH_3CF_2CFCl_2$	60	∿3.0	∿10.0	respiratory depression
(nc)	*CH_3CF_2CHFCl	38	∿3.0-4.0	∿15.0	tremors
(nc)	*$CH_2BrCFClCH_2F$	114	0.4-0.6	2.4-2.8	minimal side effects

TABLE 1 (cont.)

	Compound	bp°C	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
(nc)	*$CH_3CF_2CBrCl_2$	mp35-36	∿0.4	1.0	minimal side effects
(nc)	*$CH_3CF_2CHBr_2$	116	0.4-0.6	>3.0	minimal side effects
(nc)	*$CH_3CF_2CBr_3$				not tested
(nc)	*$CH_3CF_2CBr_2Cl$				not tested
(nc)	*$CH_3CF_2CFBrCl$	82	0.7-1.0	∿3.8	minimal side effects
(nc)	*$CH_3CF_2CFBr_2$	110	0.2-0.5	1.4-1.9	respiratory depression
(nc)	*$CH_3CF_2CF_2Br$	42	4.0-7.0	-	insufficient material to complete test
(nc)	*CH_3CF_2CHFBr	58	1.6	∿6.0	minimal side effects
	$CH_2BrCF_2CHF_2$	68			not tested
(nc)	*$CH_3CF_2CF_2H$		30-40	-	tremors

a $^{v}/_{v}$ % in oxygen

(-) signifies no reliable estimate obtained

TABLE 2

^{1}H nmr and Mass Spectral Data for Fluorinated Propanes

$C_1—C_2— C_3$

Compound	H_1	H_3	Mass Spectrum Top Mass$^+$
CF_2BrCF_2CHFBr		6.75δ,ddd,$^2J_{HF}$45.5Hz	
$CHF_2CF_2CFBr_2$	6.32δ,tt,$^2J_{HF}$50.5Hz		
$CF_2BrCF_2CFBr_2$			
CHF_2CF_2CHFBr	6.04δ,ttd,$^2J_{HF}$51.0Hz	6.56δ,ddm,$^2J_{HF}$46.0Hz	
$CFCl_2CF_2CH_2F$		4.87δ,dtd,$^2J_{HF}$44.0Hz	M-Cl
$CHFClCF_2CHFCl$	6.40δ,dt,$^2J_{HF}$46.7Hz	6.40δ,dt,$^2J_{HF}$46.7Hz	M
$CFCl_2CF_2CHFCl$		6.61δ,ddd,$^2J_{HF}$46.5Hz	M
$CFCl_2CF_2CFCl_2$			M
$CFBrClCF_2CH_2F$		4.86δ,dtd,$^2J_{HF}$44.8Hz	
$CHFClCF_2CHFBr$	6.63δ,dt,$^2J_{HF}$46.0Hz	6.40δ,dt,$^2J_{HF}$46.0Hz	
$CFBrClCF_2CHFBr$		6.95δ,ddm,$^2J_{HF}$45.5Hz	
$CHFClCF_2CFBr_2$	6.71δ,ddd,$^2J_{HF}$45.5Hz		
CH_3CF_2CHFCl	1.79δ,td,$^3J_{HF}$18.0Hz	6.07δ,dt,$^2J_{HF}$48.5Hz	
$CH_3CF_2CBrCl_2$	2.06δ,t,$^3J_{HF}$18.0Hz		
$CH_3CF_2CHBr_2$	1.95δ,t,$^3J_{HF}$18.0Hz	5.66δ,t,$^3J_{HF}$8.2Hz	M
$CH_3CF_2CBr_3$	2.14δ,t,$^3J_{HF}$17.5Hz		M-F
$CH_3CF_2CBr_2Cl$	2.14δ,t,$^3J_{HF}$17.5Hz		M-CH_3CF_2
$CH_3CF_2CFBrCl$	1.89δ,td,$^3J_{HF}$17.2Hz		M
$CH_3CF_2CFBr_2$	1.86δ,td,$^3J_{HF}$17.0Hz		M
$CH_3CF_2CF_2Br$	1.80δ,tt,$^3J_{HF}$18.0Hz		M
CH_3CF_2CHFBr	1.83δ,td,$^3J_{HF}$18.5Hz	6.38δ,dt,$^2J_{HF}$49.0Hz	M
$CH_2BrCF_2CHF_2$	3.70δ,tt,$^3J_{HF}$14.5Hz	6.0δ,tt,$^2J_{HF}$53.5Hz	M
$CH_3CF_2CF_2H$	1.67δ,tm,$^3J_{HF}$17.8Hz	5.62δ,tt,$^2J_{HF}$ 53.0Hz	M-CH_3

(cont.)

TABLE 2 (cont.)

Compound	H_1	H_3	Mass Spectrum Top Mass$^+$
$CFBrClCF_2CFBr_2$			
$CCl_2{=}CFCH_2F$		5.10δ,dd,$^2J_{HF}$47.0Hz	M
$CHCl_2CF_2CH_2F$	5.95δ,td,$^3J_{HF}$8.0Hz	4.80δ,dt,$^2J_{HF}$44.1Hz	M
$CHFBrCF_2CH_2F$	6.51δ,dm,$^2J_{HF}$46.0Hz	4.68δ,dm	M
$CHFBrCF_2CH_2Cl$	6.63δ,ddd,$^2J_{HF}$45.6Hz	3.91δ,t,$^3J_{HF}$11.8Hz	M
$CHFBrCF_2CH_2Br$	6.62δ,ddd,$^2J_{HF}$45.6Hz	3.72δ,t,$^3J_{HF}$12.0Hz	M
$CH_2ClCF_2CH_2F$	3.76δ,td,$^3J_{HF}$12.0Hz	4.66δ,tt,$^2J_{HF}$44.0Hz	
$CH_2FCFClCH_2Cl$	4.65δ,m	3.86δ,m	
$CH_2ClCF_2CH_2Cl$	3.86δ,t,$^3J_{HF}$11.8Hz	3.86δ,t,$^3J_{HF}$11.8Hz	
$CH_2BrCF_2CH_2F$	3.69δ,td,$^3J_{HF}$12.5Hz	4.70δ,dt,$^2J_{HF}$43.3Hz	
$CH_2BrCF_2CH_2Br$	3.81δ,t,$^3J_{HF}$12.5Hz	3.81δ,t,$^3J_{HF}$12.5Hz	
$CH_2BrCFClCH_2F$	3.92δ,m	4.90δ,m	
$CH_3CF_2CCl_3$	2.04δ,t,$^3J_{HF}$18.0Hz		
$CH_3CF_2CFCl_2$	1.94δ,td,$^3J_{HF}$18.0Hz		

Bromination of 1,1,2,2,3-pentafluoropropane

The pentafluoropropane (75g) and bromine (60cm^3) were vaporised simultaneously in a glass furnace tube at 400-480° to give a product mixture (17g) collected via a water-cooled condenser. Considerable pyrolysis was observed. Separation of the product by g.l.c. (SE 30) gave (i) 1-bromo-1,2,2,3,3-pentafluoropropane nmr/ir, (ii) 1,3-dibromo-1,2,2,3,3-pentafluoropropane bp 98° [Found: C,12.8; H,0.5; Br,52.8%. $C_3HBr_2F_5$ requires C,12.3; H,0.3; Br,54.8%] nmr, (iii) 1,1-dibromo-1,2,2,3,3-pentafluoropropane nmr, (iv) 1,1,3-tribromo-1,2,2,3,3-pentafluoropropane nmr, and (v) 1,1,2-tribromotrifluoroethane (identified by ir comparison with an authentic sample).

Chlorination and bromination of 1-chloro-1,2,2,3-tetrafluoropropane

The propane (17.6g), prepared from the tosyl ester of 3-chloro-2,2,3,-trifluoropropanol *[3]* and potassium fluoride, was chlorinated (17g Cl_2) by a previously described procedure *[2]* to give a product (18.1g). Fractional distillation gave fraction A (4.3g) boiling range 77-85°, fraction B (7.2g) boiling range 86-93°, and a residue (6.6g). Separation of fraction A by g.l.c. (SE 30, 40-110°) gave (i) starting material (116mg), (ii) 1,1-dichloro-1,2,2,3-tetrafluoropropane (195mg) bp 73° *[Found: C, 19.5; H,1.4%. $C_3H_2Cl_2F_4$ requires C,19.5; H,1.1%]* nmr/ms, (iii) a mixture of components (ii) and (iv) (418mg), (iv) 1,3-dichloro-1,2,2,3-tetrafluoropropane (264mg) bp 70° *[Found: C,19.4; H,1.1%. $C_3H_2Cl_2F_4$ requires C,19.5; H,1.1%]* nmr/ms, (v) 1,1,3-trichloro-1,2,2,3-tetrafluoropropane (210mg) bp 96.5° nmr/ms, and (vi) 1,1,3,3-tetrachlorotetrafluoropropane (10mg) bp 116.5° nmr/ms.

The propane (8.3g) was also brominated (6cm^3 Br_2) at 440°, and the product (6.6g) fractionated to give fraction A (1.4g, essentially starting material) boiling range 52-62°, fraction B (2.6g) boiling range 63-92°, and a residue (1.7g). Separation of fraction B and the residue by g.l.c. gave (i) starting material (200mg), (ii) 1-bromo-1-chloro-1,2,2,3-tetrafluoropropane (ca. 1.0g) bp 94° *[Found: C,16.0; H,1.0; Cl,14.5; Br,35.9%. $C_3H_2BrClF_4$ requires C,15.8; H,0.9; Cl,15.4; Br,34.6%]* nmr, (iii) 1-bromo-3-chloro-1,2,2,3-tetrafluoropropane (ca. 1.0g) *[Found: C,16.0; H,1.0; Cl,14.7; Br,36.2%. $C_3H_2BrClF_4$ requires C,15.8; H,0.9; Cl,15.4; Br,34.6%]* nmr, (iv) a mixture of 1,1-dibromo-3-chloro-1,2,2,3-tetrafluoropropane and 1,3-dibromo-1-chloro-1,2,2,3-tetrafluoropropane (600mg) bp 137° *[Found: C,11.6; H,0.3; Cl,11.2%. $C_3HBr_2ClF_4$ requires C,11.8; H,0.3; Cl,11.4%]* nmr, and (v) 1,1,3-tribromo-3-chloro-1,2,2,3-tetrafluoropropane (100mg) *[Found: C,8.8; H,0.1; Cl,8.1%. $C_3Br_3ClF_4$ requires C,9.4; H,0.0; Cl,9.1%]* nmr.

Preparation of 1,1-dichloro-2,2,3-trifluoropropane

The tosyl ester (254g) of 3,3-dichloro-2,2-difluoropropanol *[3]* was heated to 170° with anhydrous potassium fluoride (108g) and ethylene glycol (500cm^3), and the distillate (77g) washed with water and dried ($MgSO_4$). Separation of a small portion by g.l.c. (carbowax, 120°) gave (i) 1,1-dichloro-2,3-difluoro-prop-1-ene (2.5g) bp 92° *[Found: C,21.7; H,1.8; Cl,42.4%. $C_3H_2Cl_2F_2$ requires C,21.6; H,1.8; Cl,42.6%]* nmr/ms, and (ii) 1,1-dichloro-2,2,3-trifluoropropane (0.75g) bp 90° *[Found: C,24.6; H,1.5; Cl,47.5%. $C_3H_3Cl_2F_3$ requires C,24.5; H,1.4; Cl,48.2%]* nmr/ms.

Preparation of 1-bromo-1,2,2,3-tetrafluoropropane

The tosyl ester (35.5g) of 3-bromo-2,2,3-trifluoropropanol [3] was heated to 180° with potassium fluoride (8.7g) and ethylene glycol ($40cm^3$), and the distillate (10.7g) washed with water and dried ($MgSO_4$). The dried product (7.5g) was separated by g.l.c. (SE 30, 90°) to give (i) 1-bromo-1,2,2,3-tetrafluoropropane (4.2g) bp 75° [Found: C,18.8; H,1.7%. $C_3H_3BrF_4$ requires C,18.5; H,1.5%] nmr/ms, (ii) 1-bromo-3-chloro-1,2,2-trifluoropropane (0.65g) bp 110° [Found: C,17.6; H,1.6%. $C_3H_3BrClF_3$ requires C,17.1; H,1.4%] nmr/ms, and (iii) 1,3-dibromo-1,2,2-trifluoropropane (0.35g) bp 129° [Found: C,14.8; H,1.3%. $C_3H_3Br_2F_3$ requires C,14.1; H,1.2%] nmr/ms.

Fluorination of 1,2,2-trichloro-3-fluoropropane

The propane (92g), prepared by the addition of chlorine to 2-chloroallyl fluoride, was added dropwise to antimony dichloridetrifluoride (from 150g SbF_3) at 100°, and the distillate (13.5g) separated by g.l.c. to give (i) 1-chloro-2,2,3-trifluoropropane bp ~60° [Found: C,27.3; H,2.9; Cl,27.1%. $C_3H_4ClF_3$ requires C,27.2; H,3.0; Cl,26.8%] nmr, (ii) 1,2-dichloro-2,3-difluoropropane bp 94.5° [Found: C,24.0; H,2.7; Cl,47.5%. $C_3H_4Cl_2F_2$ requires C,24.3; H,2.7; Cl,47.3%] nmr, and (iii) 1,3-dichloro-2,2-difluoropropane bp 66° [Found: C,24.0; H,2.8; Cl,47.7%. $C_3H_4Cl_2F_2$ requires C,24.3; H,2.7; Cl,47.3%] nmr.

Fluorination of 1,2-dibromo-2-chloro-3-fluoropropane

The propane (180g), prepared by the addition of bromine to 2-chloroallyl fluoride, was added dropwise to antimony dichloridetrifluoride (from 111g SbF_3) at 110°, and a portion of distillate (82.1g) separated by g.l.c. (SE 30, 100°) to give (i) 1-bromo-2,2,3-trifluoropropane bp 79-80° [Found: C,20.2; H,2.4%. $C_3H_4BrF_3$ requires C,20.4; H,2.3%] nmr, (ii) 1,3-dibromo-2,2-difluoropropane bp 139° [Found: C,15.3; H,1.7%. $C_3H_4Br_2F_2$ requires C,15.1; H,1.7%] nmr, and (iii) 1-bromo-2-chloro-2,3-difluoropropane bp 114° [Found: C,18.7; H,2.1; Cl,17.7%. $C_3H_4BrClF_2$ requires C,18.8; H,2.1; Cl,18.2%] nmr.

Chlorination and fluorination of 1-chloro-2,2-difluoropropane

The propane (100g) was chlorinated (125g Cl_2) by a previously described procedure *[2]* to give a product (144.5g) shown by g.l.c. (SE 30, 100°) to be mainly one compound. Purification of a small portion by g.l.c. gave 1,1,1-trichloro-2,2-difluoropropane bp 100° *[*Found: C,20.4; H,1.8; Cl,57.9%. $C_3H_3Cl_3F_2$ requires C,19.8; H,1.7; Cl,57.7%*]* nmr. Chlorine gas was bubbled slowly through a mixture of the crude trichloropropane (45g), antimony trifluoride (18.3g) and antimony pentachloride (1.8g) at ambient temperature until white fumes were evolved. The reaction mixture was then heated to 100° for 30 min. under reflux, and the distilled product (24.1g) boiling range 60-66° shown by g.l.c. to be ∿90% one compound. A small portion was separated by g.l.c. to give 1,1-dichloro-1,2,2-trifluoropropane bp 60° *[*Found: C,22.0; H,1.2; Cl,42.1%. $C_3H_3Cl_2F_3$ requires C,21.7; H,1.8; Cl,42.2%*]* nmr. The crude dichlorotrifluoropropane (40g) was reduced with $LiAlH_4$ (2.3g) in tetrahydrofuran (30cm^3) to give 1-chloro-1,2,2-trifluoropropane bp 38° *[*Found: C,27.8; H,2.9; Cl,26.9%. $C_3H_4ClF_3$ requires C,27.3; H,3.0; Cl,26.5%*]* nmr.

Chlorination of 1-bromo-2,2-difluoropropane

The alkane (98g) was chlorinated (43g Cl_2) by a previously described procedure *[2]*, and a portion (50g) of the product (110g) distilled to give a volatile fraction (35.4g) and a residue (10.5g). The residue was shown by g.l.c. (SE 30, 100°) to be essentially one component, and a small portion was purified by g.l.c. to give 1-bromo-1,1-dichloro-2,2-difluoropropane mp 35-36° (sublimes) *[*Found: C,16.6; H,1.2; Cl,30.8; Br,36.4%. $C_3H_3BrCl_2F_2$ requires C,15.9; H,1.3; Cl,30.8; Br,35.2%*]* nmr.

Fluorination of 1,1,2,2-tetrabromopropane

Antimony pentafluoride (140g) was added dropwise to the tetrabromopropane (117g, prepared by addition of Br_2 to propyne) at 0°. The product (16.1g) was distilled and fractionated to give

fraction	boiling range °C	wt.
1	60-66	6.55g
2	70	2.45g
3	70	1.30g
residue		2.80g

Fraction 1 was shown by g.l.c. (DEHS, 110°) to contain two components in the ratio 1:1, and was separated by g.l.c. to give (i) 1-bromo-1,2,2-

trifluoropropane bp 58° [Found: C,20.9; H,2.5%. $C_3H_4BrF_3$ requires C,20.3; H,2.3%] nmr/ms, and (ii) 1-bromo-2,2,3,3-tetrafluoropropane bp 68° [Found: C,18.7; H,1.7; Br,39.9%. $C_3H_3BrF_4$ requires C,18.5; H,1.6; Br,40.9%] nmr/ms. The residue contained predominantly one component, and was purified by g.l.c. to give 1,1-dibromo-2,2-difluoropropane bp 116° [Found: C,15.3; H,1.6; Br,67.5%; $C_3H_4Br_2F_2$ requires C,15.1; H,1.7; Br,67.2%] nmr/ms. During the addition of antimony pentafluoride, a small quantity of a volatile liquid was collected in an attached trap at -80°, and was shown to be pure by g.l.c. The compound was tentatively identified by nmr/ms as 1,1,2,2-tetrafluoropropane.

Chlorination and fluorination of 1,1-dibromo-2,2-difluoropropane

The propane (77.6g), prepared as above, was chlorinated (23g Cl_2) by a previously described procedure [2] , and the product (82g) dissolved in a small quantity of diethyl ether to reduce its tendency to solidify. Separation by g.l.c. (SE 30, 135°) gave, in addition to ether and starting material, (i) 1,1-dibromo-1-chloro-2,2-difluoropropane nmr/ms and (ii) 1,1,1-tribromo-2,2-difluoropropane nmr/ms, in the ratio 2:1 resp. A crude chloroproduct (74g), prepared in this way was stirred at 140° with antimony trifluoride (63g) and antimony pentachloride (5cm^3). Addition of bromine (15cm^3) allowed a product boiling range 65-110° to distil. The product was washed (10% NaOH) to remove bromine, and the resultant clear liquid (31.0g) was fractionated to give

fraction	boiling range °C	wt.
1	76-82	4.3g
2	83-90	5.6g
3	91-104	4.0g
4	105-110	7.7g
residue		

Fraction 1 was separated by g.l.c. (SE 30, 90°) to give (i) 1,1-dichloro-1,2,2-trifluoropropane (0.4g), identified by ir comparison with an authentic sample, and (ii) 1-bromo-1-chloro-1,2,2-trifluoropropane (2.0g) bp 82° [Found: C,17.1; H,1.4; Br,38.7%. $C_3H_3ClBrF_3$ requires C,17.0; H,1.4; Br,37.8%] nmr/ms. Fraction 4 was separated by g.l.c. (SE 30, 100-105°) to give (i) a further quantity (0.6g) of 1-bromo-1-chloro-1,2,2-trifluoropropane, (ii) 1,1,1-trichloro-2,2-difluoropropane (~0.6g), identified by ir comparison with an authentic sample, (iii) 1,1-dibromo-1,2,2-trifluoropropane (~0.6g) bp 110° nmr/ms, and (iv) 1-bromo-1,1-dichloro-2,2-

difluoropropane (0.7g), identified by ir comparison with an authentic sample. A crude sample of 1,1-dibromo-1,2,2-trifluoropropane (37g) was further fluorinated with antimony pentafluoride (49g) at 0-25°, and from the distillate (7.4g) was isolated by g.l.c. (SE 30) a small sample of 1-bromo-1,1,2,2-tetrafluoropropane bp 42°nmr/ms.

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 volatised 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 minimal lethal concentration was similarly estimated. Further details on these tests will be published elsewhere [1].

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