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NEW INHALATION ANAESTHETICS: V. FLUORINATED BUTANES (AND BUTENES)

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SUMMARY

A range of fluorohalobutanes has been prepared for screening as potential inhalation anaesthetics by chlorination and fluorination of halogenated butanes and butenes. Surprisingly, several fluorohalobutenes were obtained as side products of the fluorination of halogenated butanes, and there was evidence of considerable rearrangement of the butane carbon skeleton. None of the compounds tested, however, gave good anaesthesia with no side effects.

INTRODUCTION

Previous papers in this series have described the syntheses of fluorinated 1,3-dioxolanes *[1]*, methyl propyl ethers *[2]*, methyl ethyl ethers *[3]*, diethyl ethers *[3]*, methyl butyl ethers *[3]*, and propanes *[4]* as potential inhalation anaesthetics. The constraints of volatility usually lead to a preference for C_2 and C_3 compounds in the search for novel inhalation anaesthetics, but this in turn considerably reduces the total number of compounds which might be considered for synthesis. On the other hand, there are many unknown and potentially volatile C_4 compounds which might be candidate anaesthetics, and in this paper therefore we describe the preparation and anaesthetic properties of a number of C_4 alkanes.

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RESULTS AND DISCUSSION

The compounds prepared in this paper were obtained from two basic reaction sequences. In the first of these, summarised in figure 1, methyl ethyl ketone was treated with phosphorus pentachloride to obtain 2,2-dichlorobutane for fluorination to 2,2-difluorobutane, but the reaction was surprisingly accompanied by the formation of large quantities of unsaturated products, at least according to gas chromatographic data. However, it was also found that2,2-dichlorobutane was to some extent unstable in the gas chromatograph and was decomposing to give the observed unsaturated compounds, so that it was not possible to determine the absolute product ratios by this means. Fluorination of the product mixture was therefore carried out in the presence of hydrogen chloride gas to obtain the maximum possible yield of 2,2-difluorobutane.

Chlorination of the difluorobutane proceeded smoothly, and was observed to be directed exclusively towards the ethyl end of the molecule, up to and including the formation of $CH_3CF_2CCl_2CCl_3$. A chlorinated mixture containing the latter as the predominant component was subsequently fluorinated with antimony trifluoride as shown in figure 1, giving $CH_3CF_2CCl_2CF_2Cl$ as the major product.

However, eight side products also resulted from this latter reaction, and their structures were not consistent with the pattern of chlorination of 2,2-difluorobutane. Three were fluorochlorobutanes, showing halogenation of carbon atoms 1,2 and 4 rather than 1,2 and 3, and four of the fluorochlorobutenes also showed halogenation of carbon atom 4. The remaining product was a fluorochloro-iso-butene, which could only have arisen by rearrangement of the basic carbon skeleton of the starting material. We would therefore tentatively suggest that the isobutene structure may be an intermediate in a rearrangement of the carbon skeleton which eventually leads to the unexpected n-butanes and n-butenes shown in figure 1.

A further interesting feature common to all eight side products but absent in the major reaction product is the presence of a CF_3— group. We have previously observed the ability of antimony halides to induce halogen migration [4], and we would therefore tentatively suggest that during the skeletal rearrangement such migration might also be promoted. The mechanism by which the proposed carbon rearrangement might occur, however, remains unclear.

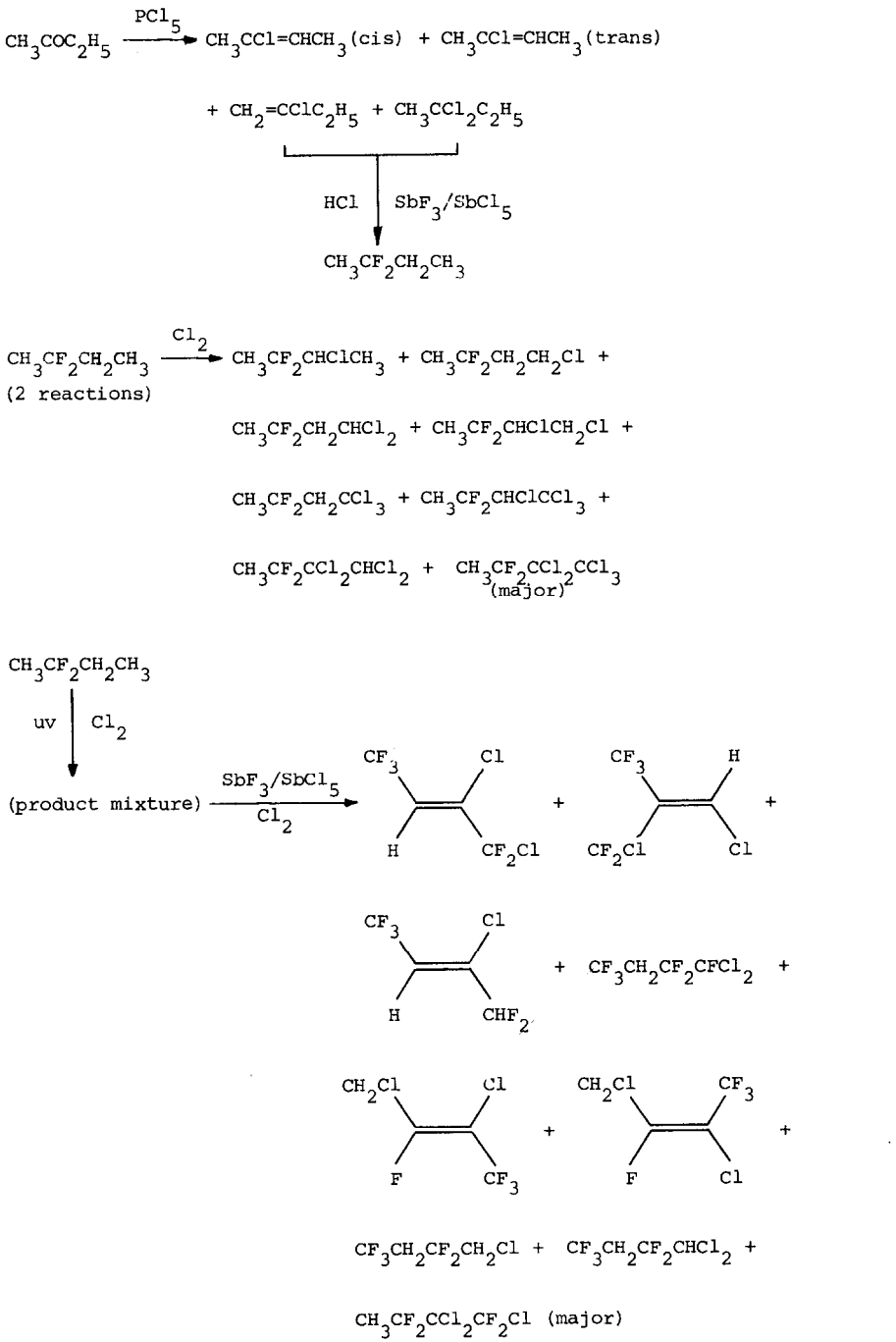

CH3COC2H5
PCl5
CH3CCl=CHCH3(cis) + CH3CCl=CHCH3(trans)
+ CH2=CClC2H5 + CH3CCl2C2H5
HCl
SbF3/SbCl5
CH3CF2CH2CH3
CH3CF2CH2CH3
Cl2
(2 reactions)
CH3CF2CHClCH3 + CH3CF2CH2CH2Cl +
CH3CF2CH2CHCl2 + CH3CF2CHClCH2Cl +
CH3CF2CH2CCl3 + CH3CF2CHClCCl3 +
CH3CF2CCl2CHCl2 + CH3CF2CCl2CCl3
(major)
CH3CF2CH2CH3
uv
Cl2
(product mixture)
SbF3/SbCl5
Cl2
CF3
Cl
H
CF2Cl
+
CF3
H
CF2Cl
Cl
+
CF3
Cl
H
CHF2
+ CF3CH2CF2CFCl2 +
CH2Cl
Cl
F
CF3
+
CH2Cl
CF3
F
Cl
+
CF3CH2CF2CH2Cl + CF3CH2CF2CHCl2 +
CH3CF2CCl2CF2Cl (major)

Figure 1

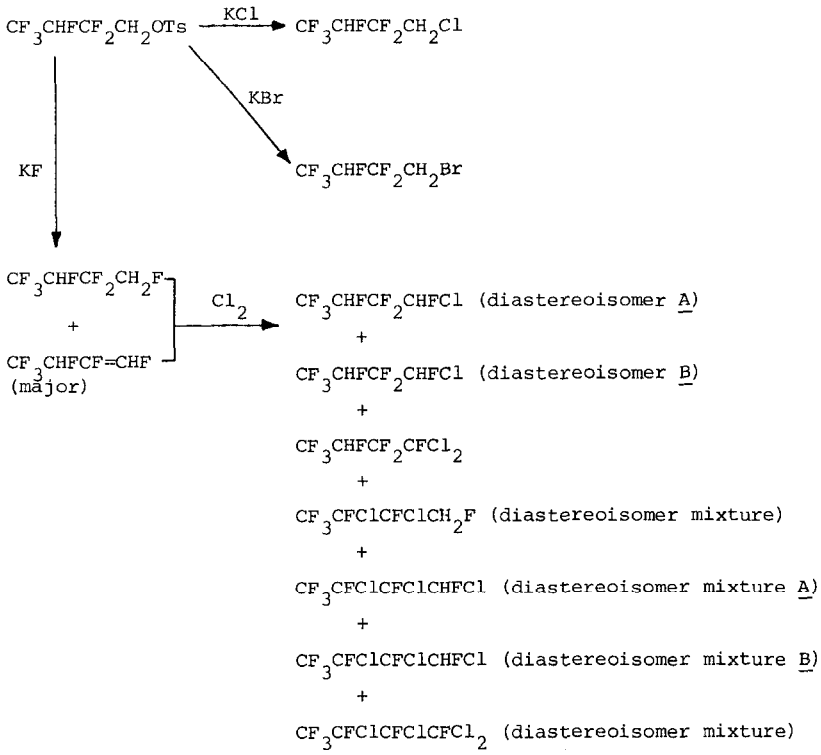


Figure 2

The second reaction sequence, summarised in figure 2, involved the reaction of the tosyl ester of 2,2,3,4,4,4-hexafluorobutanol *[3]* with potassium halides. Reaction with potassium chloride and potassium bromide afforded the corresponding chloro- and bromohexafluorobutanes in good yield, but reaction with potassium fluoride unexpectedly gave mainly a hexafluorobutene, the desired heptafluorobutane being only a minor product. This confirms our previous observation that potassium fluoride can, under favourable circumstances, behave as a dehydrofluorinating agent for halogenated alkanes *[4]*. Chlorination of a mixture of the hexafluorobutene and heptafluorobutane gave a product mixture from which it was possible to obtain several diastereoisomeric pairs, including in one case the diastereoisomers separately, as shown in figure 2.

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.

None of the compounds tested gave good anaesthesia with no side effects, unsaturated compounds being generally associated with delayed death, and other compounds causing either convulsions or marked respiratory depression.

EXPERIMENTAL

Physical Methods

Boiling points were determined by the Siwoloboff method, and are uncorrected. Gas chromatography was carried out using silicone gum (SE 30), diethyl hexyl sebacate (DEHS), dinonyl phthalate (DNP), or carbowax on chromosorb W. ^{1}H nmr, ^{19}F nmr, ir and mass spectra were recorded as previously described [1].

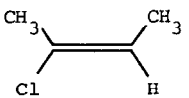
Preparation, chlorination and fluorination of 2,2-difluorobutane

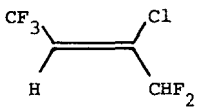
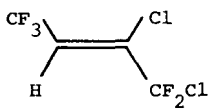
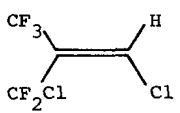
Methyl ethyl ketone (1224cm^3) was added dropwise to phosphorous pentachloride (2836g) over 5hrs at ambient temperature and the product added dropwise to water (4L). The organic layer was washed with water (2L) and dried ($CaCl_2$) to give a clear liquid (ca. 900g). Separation of a small portion by g.l.c. (SE 30, 30-80°) gave (i) 2-chlorobut-1-ene, ^{1}H nmr 1.18 δ(t,3H,CH_3), 2.46 δ(q,2H,$C\underline{H}_2CH_3$), 5.26 δ(t,2H,CH_2=), (ii) cis-2-chlorobut-2-ene [Found: C,53.3; H,8.0%. C_4H_7Cl requires C,53.0; H,7.7%] ^{1}H nmr 1.66 δ(dm,3H,CH_3CH), 2.03 δ(m,3H,CH_3CCl), 5.65 δ(qm,1H,CH=), homoallylic coupling between methyl groups ∿1Hz, (iii) trans-2-chlorobut-2-ene [Found: C,53.3; H,8.0%. C_4H_7Cl requires C,53.0; H,7.7%] ^{1}H nmr 1.78 δ(dm,3H,$C\underline{H}_3CH$), 2.17 δ(m,3H,$C\underline{H}_3CCl$), 5.66 δ(qm,1H,CH=) homoallylic coupling between methyl groups ∿1.5Hz, and (iv) 2,2-dichlorobutane, identified by ir spectroscopy. Ratio of products approximately 4:7:3:11 resp. by g.l.c.

TABLE 1

Biological Properties of Some Halogenated Butanes

a. v/v % in oxygen. b. mixture of diastereoisomers. c. cis and trans. (-) no reliable estimate obtained.

	Compound	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
		2	> 4	(no comments available)
	$CH_3CF_2CH_2CH_3$	∿8.0	21.6	lung damage
	$CH_3CF_2CHClCH_3$	1-1.5	∿8.0	not relaxed
	$CH_3CF_2CH_2CH_2Cl$	3.0	6.0	lung damage
nc	$CF_3CHFCF{=}CHF$	6.0	-	delayed death
	$CF_3CHFCF_2CH_2F$	4.5	11.4	marked respiratory depression
nc	$CF_3CHFCF_2CH_2Cl$	0.5-0.8	2.0	marked respiratory depression
nc	$CF_3CHFCF_2CH_2Br$	0.3	0.9	marked respiratory depression
nc	CF_3CHFCF_2CHFCl[b]	0.8	2.0	marked respiratory depression
nc	$CF_3CHFCF_2CFCl_2$	1.8	>4	poor anaesthesia

nc	$CF_3CFClCFClCH_2F$[b]	0.9	1.8-2.7	convulsant
nc	$CF_3CH_2CF_2CH_2Cl$	0.4-0.7	1.5-1.9	tremors
nc	$CF_3CH_2CF_2CHCl_2$	0.3-0.6	1.0-1.3	convulsant
nc	$CF_3CH_2CF_2CFCl_2$	-	-	convulsant
nc	$CF_3CCl{=}CFCH_2Cl$[c]	-	-	no effect at 0.2%
nc		-	-	no effect at 0.2%
nc		-	-	convulsant, delayed death; lung damage at 1.9%
		-	-	delayed death and lung damage at 1.9%
nc	$CH_3CF_2CCl_2CF_2Cl$	1.0	3.0	convulsant

A portion (323g) of the product mixture was added dropwise to stirred antimony trifluoride (466g) and antimony pentachloride ($20cm^3$) at ambient temperature, and anhydrous hydrogen chloride gas passed through the stirred reaction mixture. Fractional distillation gave fraction A (ca. 70g) boiling range 28-32°, essentially one compound by g.l.c., and fraction B (ca. 70g) boiling range 33-64°, shown by ir to be essentially a mixture of cis and trans 2-chlorobut-2-ene. A portion of fraction A was purified by g.l.c. to give 2,2-difluoropropane bp 28-30°, ^{1}H nmr 1.53δ(t, 3H,CH_3CF_2,$^3J_{HF}$18.5Hz), 1.0δ(t,3H,$C\underline{H}_3CH_2$), 1.83δ(tq,2H,CH_2,$^3J_{CH_2CF_2}$16.0Hz).

The difluorobutane (200g) was chlorinated by a previously described technique [1] (160g Cl_2), and a portion of the product separated by g.l.c. (SE 30) to give (i) 2-chloro-3,3-difluorobutane bp 72° [Found: C,37.8; H,6.1; Cl,28.0%. $C_4H_7ClF_2$ requires C,37.4; H,5.4; Cl,27.6%] ^{1}H nmr 1.61δ (d,3H,CH_3CH), 1.76δ(t,3H,CH_3CF_2,$^3J_{HF}$18.5Hz), 4.09δ(m,1H,CHCl), (ii) 1-chloro-3,3-difluorobutane bp 93° [Found: C,37.8; H,5.6; Cl,28.2%. $C_4H_7ClF_2$ requires C,37.4;H,5.4; Cl,27.6%] ^{1}H nmr 1.62δ(t,3H,CH_3,$^3J_{CH_3CF_2}$18.0Hz), 2.32δ(tt,2H,$C\underline{H}_2CF_2$,$^3J_{CH_2CF_2}$,14.5Hz), 3.62δ(t,2H,CH_2Cl), (iii) 1,1-dichloro-3,3-difluorobutane bp 116° [Found: C,30.2; H,4.7; Cl,43.6%. $C_4H_6Cl_2F_2$ requires C,29.4; H,3.7; Cl,43.6%] ^{1}H nmr 1.70δ(t,3H,CH_3,$^3J_{HF}$18.5Hz),2.85δ (td,2H,CH_2,$^3J_{CH_2CF_2}$14.5Hz), 5.90δ(t,1H,$CHCl_2$), and (iv) 1,2-dichloro-3,3-difluorobutane ^{1}H nmr 1.81δ(t,3H,CH_3 $^3J_{HF}$18.5Hz), 3.60-4.20δ(m,3H,CH_2Cl and CHCl). A second sample of the difluorobutane (110g) was also chlorinated (726g Cl_2) to give a product (303g), a small portion of which was separated by g.l.c. to give four compounds tentatively identified by nmr as (i) 1,1,1-trichloro-3,3-difluorobutane, ^{1}H nmr 1.70δ(t,3H, CH_3,$^3J_{HF}$ 20.0Hz) 3.28δ(t,2H,CH_2,$^3J_{HF}$12.5Hz) (ii) 1,1,1,2-tetrachloro-3,3-difluorobutane, ^{1}H nmr 1.80δ(t,3H,CH_3,$^3J_{HF}$20.0Hz),4.70δ(dd,1H, CHCl,$^3J_{HF}$ 6.0 and 8.5Hz) (iii) 1,1,2,2-tetrachloro-3,3-difluorobutane, ^{1}H nmr 1.92δ (t,3H,CH_3 $^3J_{HF}$19.0Hz), 6.10δ(s,1H,$CHCl_2$) and (iv) 1,1,2,2,2-pentachloro-3, 3-difluorobutane (major product), ^{1}H nmr 1.98δ(t,3H,CH_3 $^3J_{HF}$19.0Hz).

The crude product mixture (300g) from the latter chlorination was added dropwise to a stirred mixture of antimony trifluoride (340g) and antimony pentachloride ($20cm^3$) at ambient temperature. Chlorine gas (40g) was passed through the reaction mixture, and the product (146g) boiling range 80-120° collected by distillation. The product was washed with water ($150cm^3$), dried ($MgSO_4$) and a portion of the resulting pale orange liquid (135g) separated by g.l.c. (SE 30) to give (i) 1,2-dichloro-1,1,4,

4,4-pentafluorobut-2-ene [Found: C,22.2; H,0.9%. $C_4HCl_2F_5$ requires C,22.4; H,0.5%] ^{1}H nmr 6.60δ(q,CH,$^3J_{HF}$6.5Hz), ^{19}F nmr 58.05 ppm (from $CFCl_3$)(CF_2Cl–), 60.96 ppm (CF_3,$^5J_{CF_3-CF_2Cl}$1.3Hz), CF_3– and CF_2Cl– trans from nmr, (ii) 1,3-dichloro-3,3-difluoro-2-trifluoromethylprop-1-ene ^{1}H nmr 3.15δ(t,CH,$^4J_{CH-CF_2}$ <1.0Hz) with a consistent mass spectral fragmentation pattern, H- and CF_2Cl- trans, (iii) 2-chloro-1,1,4,4,4-pentafluorobut-2-ene [Found: C,26.3; H,1.4%. $C_4H_2ClF_5$ requires C,26.6; H,1.1%] ^{1}H nmr 6.00δ(t,1H,CHF_2-,$^2J_{HF}$ 53.0Hz), 6.42δ(q,1H,CH=,$^3J_{HF}$6.0Hz), ^{19}F nmr (from $CFCl_3$) 60.86 ppm (CF_3), 119.13 ppm (CF_2H), CF_3- and Cl- cis, (iv) 1,1-dichloro-1,2,2,4,4,4-hexafluorobutane [Found: C,20.6; H,0.9%. $C_4H_2Cl_2F_6$ requires C,20.4; H,0.9%] ^{1}H nmr 3.09δ(tq,2H,CH_2,$^3J_{CH_2CF_2}$15.5Hz), ^{19}F nmr (from $CFCl_3$) 61.62 ppm (CF_3), 110.83 ppm (CF_2), 74.52 ppm ($CFCl_2$), (v) 1-chloro-2,2,4,4,4-pentafluorobutane [Found: C,26.4; H,2.2%. $C_4H_4ClF_5$ requires C,26.3; H,2.2%] ^{1}H nmr 2.96δ(tq,2H,CH_2,$^3J_{CH_2CF_2}$14.5Hz), 3.80δ(t,2H,CH_2Cl,$^3J_{HF}$12.0Hz), ^{19}F nmr (from $CFCl_3$) 62.70 ppm (CF_3), 98.69 ppm (CF_2), (vi) 1,3-dichloro-2,4,4,4-tetrafluorobut-2-ene, CF_3/F trans, ^{1}H nmr 4.36δ(d,2H,CH_2Cl,$^3J_{HF}$21.3Hz), ^{19}F nmr (from $CFCl_3$) 62.14 ppm (CF_3). 89.97 ppm (CF),$^4J_{CF_3-F}$9.47Hz, (vii) 1,3-dichloro-2,4,4,4-tetrafluorobut-2-ene, CF_3/F cis, [Found: C,24.4; H,1.2%. $C_4H_2Cl_2F_4$ requires C,24.4; H,1.0%] ^{1}H nmr 4.35δ(d,2H,CH_2Cl,$^3J_{HF}$ 20.0Hz), ^{19}F nmr (from $CFCl_3$) 63.56 ppm (CF_3), 100.54 ppm (CF), (viii) 1,1-dichloro-2,2,4,4,4-pentafluorobutane [Found: C,22.4; H,1.4%. $C_4H_3Cl_2F_5$ requires C,22.1;H,1.4%] ^{1}H nmr 3.08 δ(tq,2H,CH_2,$^3J_{CH_2CF_2}$15.0Hz), 5.80δ(t,1H, CH,$^3J_{HF}$6.5Hz), ^{19}F nmr (from $CFCl_3$) 61.92 ppm (CF_3), 105.33 ppm (CF_2), and (ix) 1,2,2,–trichloro-1,1,3,3-tetrafluorobutane (major product) [Found: C, 20.7; H,1.2; Cl,44.0%. $C_4H_3Cl_3F_4$ requires C,20.7; H,1.3; Cl,45.3%] ^{1}H nmr 1.98δ(tt,3H,CH_3,$^3J_{HF}$18.0Hz), ^{19}F nmr (from $CFCl_3$) 58.75 ppm (CF_2Cl), 93.89 ppm (CF_2).

All compounds had consistent mass spectral fragmentation patterns.

Preparation of halogenated butanes from 2,2,3,4,4,4-hexafluorobut-1-yl tosylate

The tosylate (73.2g), prepared from 2,2,3,4,4,4-hexafluorobutan-1-ol [3], was heated at 185° with potassium fluoride (30g) and ethylene glycol (148cm^3), and the product (25.8g) allowed to distil as it formed. A portion (2.25cm^3) was separated by g.l.c. (carbowax, 26°) to give (i) 1,2, 3,4,4,4- hexafluorobut-1-ene (2.3g) [Found: M(mass spec)164. $C_4H_2F_6$ requires M(mass spec)164] ^{1}H nmr 4.92δ(dm,1H,CHF,$^2J_{HF}$46.0Hz), 5.27δ(dm,1H, CHF=,$^2J_{HF}$46.0Hz), and (ii) 1,2,2,3,4,4,4-heptafluorobutane (0.5g) [Found:

M(mass spec)151. $C_4H_3F_7$ requires M-CH_2F(mass spec)151] ^1H nmr 4.26-5.30δ (m), fragmentation pattern of mass spectrum consistent with proposed structure. Similarly prepared were 1-chloro-2,2,3,4,4,4-hexafluorobutane [Found: C,24.3; H,1.7%. M(mass spec)200. $C_4H_3ClF_6$ requires C,24.0; H,1.5%. M(mass spec)200] ^1H nmr 3.85δ(td,2H,CH_2Cl,$^3J_{HF}$11.3Hz), 5.05δ(dm,1H,CHF,$^2J_{HF}$ 43.0Hz), ^{19}F nmr (from $CFCl_3$) 74.72 ppm (CF_3), 114 ppm and 115 ppm (each F of CF_2), 213.93 ppm (CFH), and 1-bromo-2,2,3,4,4,4-hexafluorobutane bp86°

[Found: C,19.7; H,1.4%. M(mass spec)244. $C_4H_3BrF_6$ requires C,19.7; H, 1.2%. M(mass spec)244] ^1H nmr 3.24δ(td,2H,CH_2Br,$^3J_{HF}$12.0Hz), 5.20δ(dm,1H, CHF), ^{19}F nmr (from $CFCl_3$) 74.82 ppm (CF_3), 110 and 111 ppm (each F of CF_2), 212.20 ppm (CFH).

A mixture (60g) of the hexafluorobutene and heptafluorobutane, in the approximate ratio 1:1, was chlorinated (29g Cl_2) with a medium pressure mercury vapour lamp at 0°, and the product mixture separated by g.l.c. (SE 30, DEHS, DNP) to give (i) one diastereoisomer of 1-chloro-1,2,2,3,4,4,4-heptafluorobutane ^1H nmr 5.18δ(dm,1H,CHF), 6.32δ(dm,1H,CHFCl), (ii) a second diastereoisomer of (i), ^1H nmr as for (i) but with different splitting pattern, (iii) 1,1-dichloro-1,2,2,3,4,4,4-heptafluorobutane [Found: M(mass spec)217. $C_4HCl_2F_7$ requires M-Cl(mass spec)217] ^1H nmr 5.30δ(dm,1H,CHF), ^{19}F nmr (from $CFCl_3$) 74.5 ppm (CF_3), 73.6 ppm ($CFCl_2$), 115.1 and 124.1 ppm (each F of CF_2), 209.5 ppm (CH_2F), (iv) a mixture of diastereoisomers of 2,3-dichloro-1,2,3,4,4,4-hexafluorobutane [Found: M (mass spec)201. $C_4H_2Cl_2F_6$ requires M-CH_2F(mass spec)201] ^1H nmr 4.83δ (dd,2H,CH_2F,$^2J_{HF}$45.5Hz), ^{19}F nmr (from $CFCl_3$) 76.11 ppm (CF_3). 127.4, 131.1 and 131.7 ppm (C<u>F</u>Cl<u>C</u>FCl), 223.4 ppm (CH_2F), (v) a mixture of diastereoisomers of 1,1,2,3-tetrachlorohexafluorobutane (from ^{19}F nmr) [Found: M(mass spec)267. $C_4Cl_4F_6$ requires M-Cl(mass spec)267] ^1H nmr no signal, (vi) a mixture of diastereoisomers of 1,2,3-trichloro-1,2,3,4,4,4-hexafluorobutane ^1H nmr 6.65δ(dm,CHFCl,$^2J_{HF}$47.0Hz), ^{19}F nmr 75.34 and 75.76 ppm (CF_3), 121.4 and 122.5 ppm (CFCl), 128.7 and 129.6 ppm (CFCl), 140.8 and 142.7 ppm (CHFCl), and (vii) a second mixture of diastereoisomers of (vi), ^1H nmr 6.54δ(dm,CHFCl,$^2J_{HF}$46.5Hz), ^{19}F nmr 75.6 ppm (CF_3), 126.6 and 129.3 ppm (CFCl), 129.3 and 132.1 ppm (CFCl), 141.0 and 144.6 ppm (CHFCl).

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 liquid tested was made up, and tested with individual mice to find a minimum anaesthetic concentration which would just give anaesthesia after thirty minutes exposure: a minimum lethal concentration was similarly estimated. Further details on the biological tests will be published elsewhere [5].

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