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NEW INHALATION ANAESTHETICS: I. FLUORINATED 1,3-DIOXOLANE DERIVATIVES

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SUMMARY

A range of fluorochlorodioxolane derivatives has been prepared by chlorination, fluorination and reduction of polyfluoroalkyl-1,3-dioxolanes, for screening as potential inhalation anaesthetics. Only 2-trifluoromethyl -1,3-dioxolane showed good anaesthesia without side effects, but is expected to be flammable at clinical concentrations.

INTRODUCTION

The synthesis of fluorinated 1,3-dioxolane derivatives as potential inhalation anaesthetics has received little attention *[1,2,3,4]* in spite of the great interest in fluoroether anaesthetics *[5]*. As part of a broader study of fluoroethers for anaesthesia, the synthesis and biological testing of a range of such compounds was therefore undertaken.

The synthesis of 2,2-di(haloalkyl)-1,3-dioxolanes from ethylene chlorohydrin and fluoro- or fluorochloroketones is relatively simple *[6]* (fig.1), and several fluorochloroacetones are readily available *[7]*.

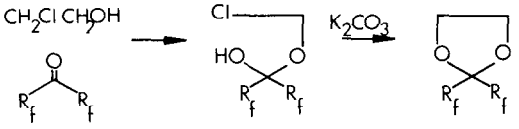

FIGURE 1

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At the same time, the fluorination of dioxan with cobalt trifluoride has recently been shown to give fluorodioxans in good yield *[8]*. It seemed reasonable, therefore to attempt a similar reaction with fluoroalkyl dioxolanes.

RESULTS AND DISCUSSION

From a fluorination of 2,2-bis(trifluoromethyl)-1,3-dioxolane with cobalt trifluoride in standard glassware we were able to isolate a difluoro-, a trifluoro-, and a tetrafluoroderivative (fig.2). Not surprisingly, the tetrafluoroderivative was biologically inert.

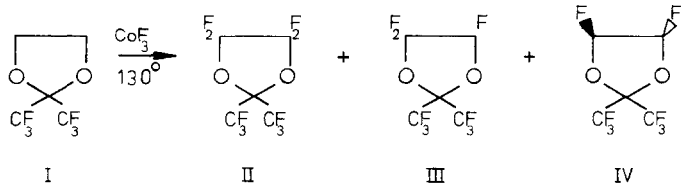


FIGURE 2

2,2-Bis(difluoromethyl)-1,3-dioxolane and 2-chlorodifluoromethyl-2-trifluoromethyl-1,3-dioxolane were then prepared from the corresponding ketones and fluorinated with cobalt trifluoride in a conventional reactor to give the products shown in fig.3.

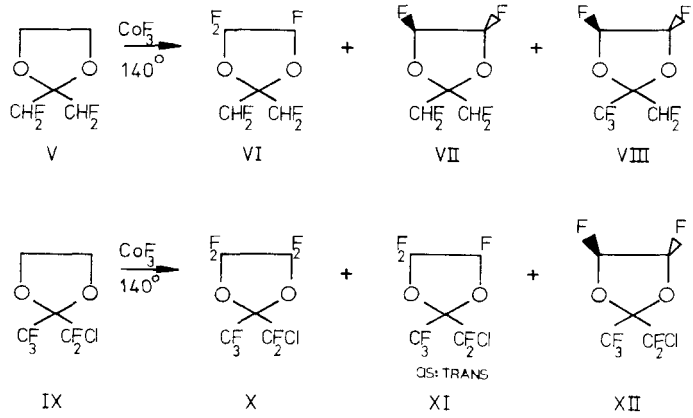
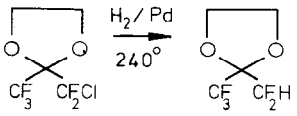
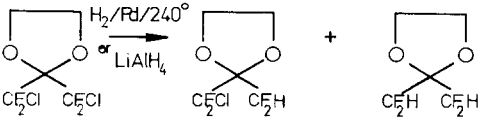


FIGURE 3

The reduction of chlorofluorocompounds is sometimes achieved by vapour phase reaction with hydrogen over palladium. Thus we have found that 2-chlorodifluoromethyl-2-trifluoromethyl-1,3-dioxolane is readily reduced to the pentafluorodioxolane (fig.4), and that 2,2-bis(chlorodifluoromethyl)-1,3-dioxolane may be reduced to its chlorotetrafluoro- analogue (fig.4). The dichlorotetrafluorodioxolane may also be reduced with $LiAlH_4$, albeit less conveniently and in poorer yield.



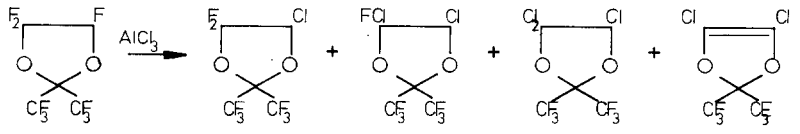
XIII



XIV XV

FIGURE 4

Anhydrous aluminium chloride has recently been shown to effect chlorine interchange for fluorine in some aliphatic α-fluoroethers [9], but the reaction does not seem to have been extended to cyclic ethers. It was therefore interesting to find that 2,2-bis(trifluoromethyl)-4,4,5-trifluoro-1,3-dioxolane underwent stepwise fluorine replacement as shown in fig.5. A similar reaction for 2,2-bis(trifluoromethyl)-4/5-difluoro-1,3-dioxolane is also shown.



XVI cis XVII trans XVIII XIX XX

FIGURE 5 (cont.)

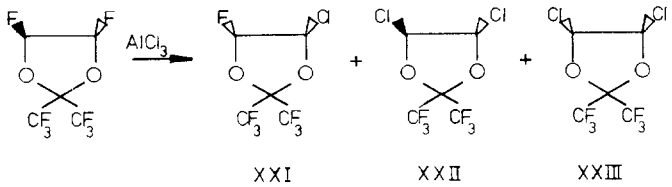


FIGURE 5

From the stereochemistry of the latter reaction, the mechanism of halogen interchange would appear to involve inversion at the α-carbon atom, suggesting an SN_2-type process. Preliminary experiments have suggested however, that the reaction may not be general for α-fluoroheterocyclic ethers, since heptafluoro-1,4-dioxan was unaltered by such treatment.

The reaction of aluminium chloride might be related to the known instability of α-haloethers, and could be analogous to the halogen exchange which occurs between antimony fluorides and α-chloroethers. At the same time, the chlorination of cyclic ethers [10] or aliphatic fluoroethers [11] proceeds smoothly to a range of chloroderivatives. An alternative approach to fluorodioxolane synthesis is therefore stepwise chlorination of partially fluorinated dioxolanes followed by halogen exchange with antimony fluoride.

We have found that stepwise chlorination and fluorination of 2,2-bis(trifluoromethyl)-1,3-dioxolane leads to almost the complete range of possible dioxolane products, and that each may be isolated by gas chromatography. Chlorination proceeds through the 4,5-dichloro- rather than the 4,4-dichloroderivative with little breakdown (fig.6).

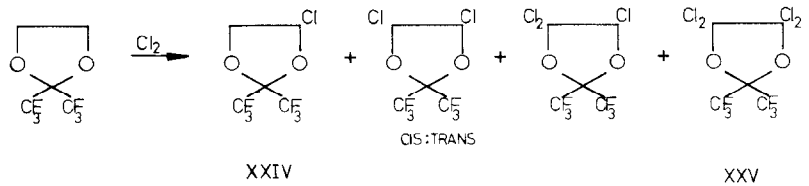


FIGURE 6

The dichloro-, trichloro- and tetrachloroderivatives are conveniently fluorinated with SbF_3Cl_2 or $SbF_3/SbCl_5$ mixture to give the products shown in fig.7.

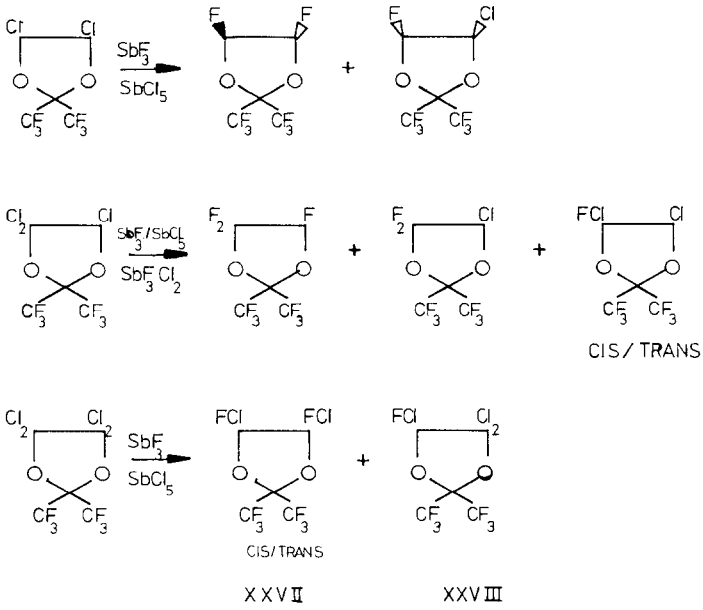


FIGURE 7

Reduction of a mixture of chlorodifluoro- and dichlorodifluoro-products with hydrogen over palladium then affords further novel dioxolanes as shown in fig.8.

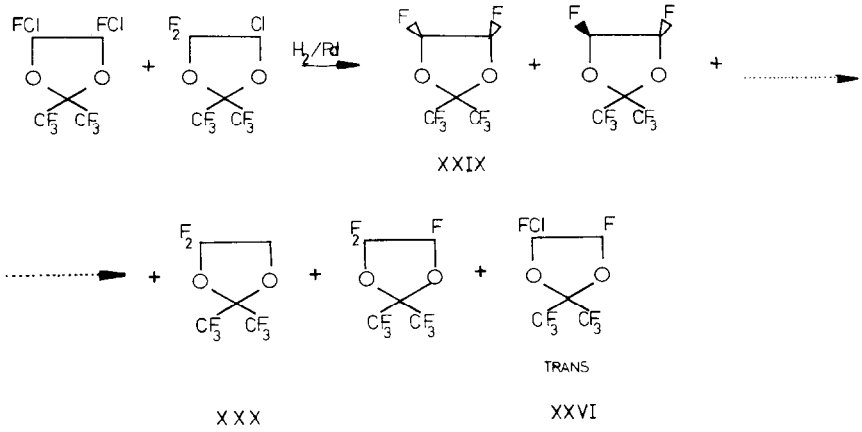


FIGURE 8

TABLE 1

Physical and Biological Data of Some Fluorinated Dioxolanes

Compd.	bp °C	Mol. Formula	Analyses	Spectra[e]	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
I	105	$C_5H_4F_6O_2$	C,H	NMR,MS	140-160mg/kg	>200mg/kg	poor anaesthesia
II		$C_5F_{10}O_2$		MS	-	-	inactive
III	55	$C_5HF_9O_2$		NMR,MS	18.3[b]	-	convulsant
IV	79	$C_5H_2F_8O_2$		NMR,MS	1.0	7.0	tremors
V	mp.40	$C_5H_6F_4O_2$	C,H	NMR,MS	150-200mg/kg	>400mg/kg	delayed death
VI		$C_5H_3F_7O_2$		NMR			not tested
VII		$C_5H_4F_6O_2$		NMR,MS			not tested
VIII		$C_5H_3F_7O_2$		NMR,MS			not tested
IX	134-8	$C_5H_4ClF_5O_2$	C,H,Cl	NMR,MS	100-120mg/kg	200mg/kg	delayed death
X	67	$C_5ClF_9O_2$		NMR,MS	-	-	inactive[c]
XI	87	$C_5HClF_8O_2$	C,H	NMR,MS	-	-	convulsions
XII	108	$C_5H_2ClF_7O_2$	C,H	NMR,MS	-	-	convulsions
XIII	123	$C_5H_5F_5O_2$	C,H	NMR,MS	80-120mg/kg	300mg/kg	poor anaesthesia
XIV	167-8	$C_5H_4Cl_2F_4O_2$	C,H,Cl	NMR,MS	-	-	delayed death at all conc[ns].
XV	154	$C_5H_5ClF_4O_2$	C,H,Cl	NMR,MS	100mg/kg	>200mg/kg	delayed death at all conc[ns].
XVI	74	$C_5HClF_8O_2$	C,H	NMR,MS	-	-	convulsant

Compd.	bp °C	Mol. Formula	Analyses	Spectra[e]	Min. Anaesthetic Concentration[a]	Min. Lethal Concentration[a]	Comments
XVII		$C_5HCl_2F_7O_2$		NMR,MS	-	-	convulsant at 3.7%
XVIII	106.5	$C_5HCl_2F_7O_2$	C,H,Cl	NMR,MS	-	3.0	convulsant
XIX	132	$C_5HCl_3F_6O_2$	C,H	NMR,MS	-	-	convulsant
XX		$C_5Cl_2F_6O_2$		MS			not tested
XXI	95.5	$C_5H_2ClF_7O_2$	C,H	NMR,MS	-	2.9	convulsant
XXII	118	$C_5H_2Cl_2F_6O_2$	C,H	NMR,MS	-	-	convulsant
XXIII		$C_5H_2Cl_2F_6O_2$		NMR,MS[d]			not tested
XXIV	114-116	$C_5H_3ClF_6O_2$	C,H	NMR,MS	0.5	1.6-1.9	delayed death
XXV	>140	$C_5Cl_4F_6O_2$	C,H		-	-	convulsant at 2.1%
XXVI		$C_5HClF_8O_2$		NMR			not tested
XXVII		$C_5Cl_2F_8O_2$	C,H	NMR,MS			not tested
XXVIII	120.5	$C_5Cl_3F_7O_2$	C,H	NMR,MS	-	-	convulsions & death at 3.2%
XXIX		$C_5H_2F_8O_2$		NMR,MS			not tested
XXX		$C_5H_2F_8O_2$		NMR,MS			not tested
XXXI	91	$C_4H_5F_3O_2$	C,H	NMR,MS	1.1	4.6	good anaesthesia
XXXII	48(2.5mm)	$C_5H_4Cl_3F_3O_2$	C,H,Cl	NMR,MS	75-100mg/kg	250-300mg/kg	poor anaesthesia

a. v/v% in oxygen, or mg/kg body weight for i.v. administration (-) signifies no reliable estimate obtained
b. maximum concentration tested c. up to 4.3% in oxygen d. cis conformation by ir comparison with XXII
e. NMR and MS spectra were consistent with the proposed structures

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 minimal lethal concentration which would just produce death in thirty minutes was also obtained, and the results are shown in table 1.

Only 2-trifluoromethyl-1,3-dioxolane gave good anaesthesia with no side effects, but the compound would be inflammable at clinical concentrations [5]. Other dioxolanes induced either convulsions or delayed death, with or without some degree of anaesthesia.

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) or 15% diethyl hexyl sebacate (DEHS) on chromosorb W. ^{1}H NMR spectra were recorded on Perkin Elmer R12/Varian A60 spectrometers at 60MHz, or on Varian HA 100/Varian HA 100D spectrometers at 100MHz. ^{19}F NMR spectra were recorded on a Varian HA 100 spectrometer at 94.1MHz or on a Perkin Elmer R12 spectrometer at 56.4MHz. 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 of authenticated compounds.

Preparation of 2-substituted-1,3-dioxolanes

Hexafluoroacetone (188g) was bubbled into stirred 2-chloroethanol (80.5g) and n-pentane($63cm^3$) and refluxed via a condenser at -80°. Potassium carbonate(138g) was then added slowly, followed by water($800cm^3$). The lower aqueous layer which formed was separated, extracted with n-pentane($3 \times 150cm^3$) and the extracts combined with the upper organic layer. The dried ($MgSO_4$) organic material was fractionated using a 6ins vacuum-jacketed column packed with glass helices to give 2,2-bistrifluoro-

methyl-1,3-dioxolane(153g;70%) b.p. 105°. [Found: C,29.2; H,2.1%, M(Mass Spec)141. $C_5H_4F_6O_2$ requires C,28.6; H,1.9% M-CF_3(Mass Spec)141] ^{1}H nmr 4.30δ(s). Similarly prepared were (XXXI) 2-trifluoromethyl-1,3-dioxolane (63%) b.p. 91°. [Found: C,33.9; H,3.5%; M(Mass Spec)141. $C_4H_5F_3O_2$ requires c,33.8; H,3.5%. M-H(Mass Spec)141] ^{1}H nmr 4.10δ(4H,s,-OCH_2CH_2O-), 5.25δ(1H,q,-$OCH(CF_3)O$-,J_{HF} 4.0Hz) 2,2-bis(difluoromethyl)-1,3-dioxolane (100%) mp 40° [Found: C,34.6; H3.2%; M(Mass Spec)123. $C_5H_6F_4O_2$ requires C,34.5; H,3.5%; M-CHF_2(Mass Spec)123] ^{1}H nmr 4.17δ(s,-OCH_2CH_2O-), ^{19}F nmr 137.5 ppm (from $CFCl_3$) (dm, J_{H-CF_2} 56.4Hz), 2-chlorodifluoromethyl-2-trifluoromethyl-1,3-dioxolane(73%) b.p. 134-8° [Found: C,27.1; H,2.0; Cl, 15.8%; M(Mass Spec)191. $C_5H_4ClF_5O_2$ requires C,26.6; H,1.8; Cl,15.5%. M-Cl(Mass Spec)191] ^{1}H nmr 4.35δ(s). 2,2-bis(chlorodifluoromethyl)-1,3-dioxolane (61%) b.p. 167-8° [Found: C,25.2; H,1.7; Cl,29.4%; M(Mass Spec) 207. $C_5H_4Cl_2F_4O_2$ requires C,24.7; H,1.6; Cl,29.2%; M-Cl(Mass Spec)207] ^{1}H nmr 4.37δ(s), and (XXXII) 2-chlorodifluoromethyl-2-dichlorofluoromethyl-1,3-dioxolane (56%) b.p. 48°/2.5mmHg [Found: C,23.3; H,1.6; Cl,41.1%; M(Mass Spec)223. $C_5H_4Cl_3F_3O_2$ requires C,23.2; H,1.5; Cl,41.0% M-Cl(Mass Spec)223] ^{1}H nmr 4.47δ(s).

Reduction of 2-chlorodifluoromethyl-2-trifluoromethyl-1,3-dioxolane

(i) The dioxolane (150g) was introduced slowly into a hydrogen stream (750cm^3/min) and passed over 5% Pd/carbon at 240° in a horizontal furnace tube 90cm x 6cm. The product (80g) was collected by water-cooled condensation and a portion (2.75cm^3) separated by g.l.c. (15% SE 30 on Chromosorb W, 100°, 120cm^3/min He) to give 2-difluoromethyl-2-trifluoromethyl-1,3-dioxolane (35%) b.p. 123° [Found: C,31.2; H,2.6%; M(Mass Spec) 191. $C_5H_5F_5O_2$ requires C,31.2; H,2.6%; M-1(Mass Spec)191] ^{1}H nmr 4.28δ (4H,s,-OCH_2CH_2O-), 5.89δ(1H,t,-CHF_2,J_{HF}51Hz)

Reduction of 2,2-bis(chlorodifluoromethyl)-1,3-dioxolane

(i) The dioxolane (84g) was reduced with H_2/Pd as above to give 51g of product which was shown by preparative g.l.c. (15% SE 30 on Chromosorb W, 100°, 40cm^3/min He) and i.r. spectroscopy to be mainly 2,2-bisdifluoromethyl-1,3-dioxolane with a trace amount of 2-chlorodifluoromethyl-2-difluoromethyl-1,3-dioxolane, by comparison with authentic samples.

(ii) The dioxolane (5g) in diethyl ether (5cm^3) was added dropwise to a stirred suspension of $LiAlH_4$(0.4g) in diethyl ether (5cm^3) and refluxed for 12hr. Excess $LiAlH_4$ was destroyed with 10% NH_4Cl (2cm^3) and the

product filtered. The filtrate was fractionated (10cm air condenser filled with glass helices) to give a fraction b.p. 160° (300mg) and a residue (3.5g) which were combined and separated by g.l.c. (15% SE 30 on Chromosorb W, 152°, 120cm^3/min He) to give (i) 2,2-bis(difluoromethyl)-1,3-dioxolane (trace) identified by i.r. spectroscopy (ii) 2-chlorodifluoromethyl-2-difluoromethyl-1,3-dioxolane (800mg) b.p. 154° [Found: C,29.3; H,2.5; Cl, 16.6%; M(Mass Spec)157. $C_5H_5ClF_4O_2$ requires C,28.8; H,2.4; Cl,16.8%; M-CHF_2(Mass Spec)157] ^{1}H nmr 4.20δ(4H,s,-OCH_2 CH_2O-), 6.0δ(1H,t,-CHF_2,J_{HF} 54 Hz), ^{19}F nmr 67.8ppm (from $CFCl_3$)(t,-CF_2Cl,J_{FF} 8.4 Hz), 135.2ppm (from $CFCl_3$)(dt,-CHF_2). (iii) starting material (2.0g) identified by i.r. spectroscopy.

Fluorination of 2,2-bis(trifluoromethyl)-1,3,-dioxolane

The dioxolane (58.6g) was fluorinated first at 170°, and then at 130°, by adding it dropwise to cobalt (III) fluoride (67g) stirred at 170° in a nitrogen stream in PTFE-sprayed glassware. The gaseous product was collected by a water-cooled condenser (36.7g) and a dry ice condenser(7.2g), and the water-cooled portion refluorinated at 130° with fresh CoF_3 to give a water-cooled fraction (18.1g) and a dry-ice-cooled fraction (7.5g). The products of each fluorination were then combined and fractionally distilled.

fraction no.	boiling range	wt.	g.l.c.
1	<50°	2.0g	(i) + (ii)
2	50-75°	1.3g	mainly (ii)
3	75-85°	1.9g	mainly (iii)
4	85-100°	3.4g	mainly (iii)
5	100-102°	3.1g	starting material (i.r.)

Fraction 1 was separated by g.l.c. (15% SE 30 on Chromosorb W, 62°, 110cm^3/min He) to give (i) perfluoro-2,2-dimethyl-1,3-dioxolane (700mg) b.p. <50° [Found: M(Mass Spec)213. $C_5F_{10}O_2$ requires M-CF_3(Mass Spec)213] and (ii) 2,2-bis(trifluoromethyl)-4,4,5-trifluoro-1,3-dioxolane (300mg) b.p. 55° [Found: M(Mass Spec)195. $C_5HF_9O_2$ requires M-CF_3(Mass Spec)195] ^{1}H nmr 6.05δ(d,-CHF, J_{HF} 62.8 Hz), ^{19}F nmr 76.5ppm (from $CFCl_3$)(1F,dp,-CF_{ax}F-), 89.3ppm (from $CFCl_3$)(1F, dd,-CFF_{eq}-), 129.6ppm (from $CFCl_3$)(1F,dm,-CHF_{ax}-,$J_{F_{ax}F_{ax}}$ 6.7 Hz, $J_{F_{ax}F_{eq}}$ 9.0 Hz). Fraction 4 was separated by g.l.c. (15% SE 30 on Chromosorb W, 80°, 110cm^3/min He) to give (iii) 2,2-

bis(trifluoromethyl)-4/5-difluoro-1,3-dioxolane (1.0g) b.p. 79° [Found: M(Mass Spec)227. $C_5H_2F_8O_2$ requires M-F(Mass Spec)227] ^{1}H nmr 6.16δ(J_{HH}O), ^{19}F nmr 81.4ppm (from $CFCl_3$)(6F, m,-CF_3), 129.4ppm(from $CFCl_3$)(2F, dm, -CHF_{ax}-, J_{FF}O).

Fluorination of 2,2-bis(difluoromethyl)-1,3-dioxolane

The dioxolane (29.6g) was fluorinated at 140° in a conventional CoF_3 reactor and the product (19.0g) collected in a dry ice trap. The product was washed with 2N NaOH, extracted with ether (3 x 25cm^3) and the extracts dried ($MgSO_4$). Ether removal by fractional distillation gave a residue, a portion of which was separated by g.l.c. to give (i) 2,2-bis(difluoromethyl) -4/5-difluoro-1,3-dioxolane (1.5g) [Found: M(Mass Spec)159. $C_5H_4F_6O_2$ requires M-CHF_2(Mass Spec)159] ^{1}H nmr 6.10δ(2H,-CHFCHF-), ^{19}F nmr 127.8ppm (from $CFCl_3$)(2F, dm,-CHFCHF-), 136.0ppm(4F, dm, -CHF_2) and (ii) a mixed peak (2.1g) which was further separated by g.l.c. (15% SE 30 on Chromosorb W, 35°) to give (iia) 2,2 -bis(difluoromethyl)-4,4,5- trifluoro-1,3-dioxolane (50%) ^{1}H nmr 6.0δ(1H,-CHFO-) ^{19}F nmr 128.1ppm (from $CFCl_3$)(1F, dm,-CHFO-, $J_{FF_{ax}}$ 7.0 Hz, $J_{FF_{eq}}$ 11.5 Hz), 75.3ppm (from $CFCl_3$)(1F, dq, -CFF_{ax}-), 89.9ppm (from $CFCl_3$)(1F, dd,-CFF_{eq}-) and (iib) 2-difluoromethyl-2-trifluoromethyl-4/5-difluoro-1,3-dioxolane (50%) [Found: M(Mass Spec) 226. $C_5H_3F_7O_2$ requires M-HF(Mass Spec)226], ^{1}H nmr 6.05δ(2H,-CHFCHF-), ^{19}F nmr 128.1ppm (from $CFCl_3$)(1F, m,-OCHF^4-, J_{FF} 3.1Hz),128.8ppm(from $CFCl_3$)(1F, m,-OCHF^5-).

Fluorination of 2-chlorodifluoromethyl-2-trifluoromethyl-1,3-dioxolane

The dioxolane (50g) was fluorinated at 140° in a conventional CoF_3 reactor to give 30.5g product which was fractionally distilled.

fraction	boiling range	weight	g.l.c.(15% SE 30,80°)
1	67-86°	4.4g	(i) + (ii)
2	86-90°	5.9g	(ii)
3	90-100°	9.3g	(ii) + (iii)
residue		8.5g	(iii)

Fraction 1 was separated by g.l.c. (15% SE 30 on Chromosorb W, 80°, 120cm^3/min He) to give (i) 2-chlorodifluoromethyl-2-trifluoromethyl-tetrafluoro-1,3-dioxolane (800mg) b.p. 67° [Found: M(Mass Spec)279. $C_5ClF_9O_2$ requires M-F(Mass Spec)279] ^{19}F nmr 81.7ppm (from $CFCl_3$)(4F, s, -CF_2CF_2-), 79.4ppm (from $CFCl_3$)(3F,-CF_3), 68.4ppm (from $CFCl_3$)(2F,-CF_2Cl)

and (ii) 2-chlorodifluoromethyl-2-trifluoromethyl-4,4,5-trifluoro-1,3-dioxolane (2.6g) b.p. 87° [Found: C,21.5; H,0.5%; M(Mass Spec)261. $C_5HClF_8O_2$ requires C,21.4; H,0.4%; M-F(Mass Spec)261] ^{1}H nmr 6.02δ(-CHF-), ^{19}F nmr 129.4ppm (from $CFCl_3$)(1F, dm,-CHF-), 75.1ppm (1F, dm,-$CF_{ax}F$-, CF_3 cis to -CFH-), 85.2ppm (1F, dm,-$CF_{ax}F$-, CF_3 trans to -CFH-), 86.1ppm (1F, dd,-$CF_{eq}F$-, CF_3 trans to -CFH-). The residue was separated by g.l.c. (15% SE 30,80°, 120cm^3/min) to give a further sample of (ii)(400mg) by i.r. and (iii) 2-chlorodifluoromethyl-2-trifluoromethyl-4/5-difluoro-1,3-dioxolane (2.6g) b.p. 108° [Found: C,23.0; H,0.7%; M(Mass Spec)227. $C_5H_2ClF_7O_2$ requires C,22.9; H,0.8%; M-Cl(Mass Spec)227] ^{1}H nmr 6.10δ(-CHFCHF-), ^{19}F nmr 127.4ppm (from $CFCl_3$)(1F, m,-CHF_{ax}-) 128.2ppm (1F, m,-CHF_{eq}-).

Reaction of 2,2-bis(trifluoromethyl)-4,4,5-trifluoro-1,3-dioxolane with $AlCl_3$

The dioxolane (13.8g) was stirred under reflux with anhydrous $AlCl_3$ for 90hr and the product (10.5g) was vacuum distilled. Fractional distillation then gave

fraction	boiling range	wt.	g.l.c.(SE 30,70°)
1	67-72°	1.8g	(i) + starting material
2	72-74°	3.5g	(i)
3	74°	2.1g	(i)
residue		2.3g	(i),(ii),(iii),(iv),(v)

Fraction 3 was found to be 2,2-bis(trifluoromethyl)-4,4-difluoro-5-chloro-1,3-dioxolane b.p. 74°. [Found: C,21.0; H,0.4%; M(Mass Spec)261. $C_5HClF_8O_2$ requires C,21.4; H,0.4% M-F(Mass Spec)261] ^{1}H nmr 6.32δ(dd), ^{19}F nmr 72.07ppm (from $CFCl_3$)(1F, dp,-$CF_{ax}F$-), 77.11ppm (1F, dm,-$CF_{eq}F$-). The residue was separated by g.l.c. (15% SE 30, 120cm^3/min He) to give a further sample of (i) (760mg), a mixture of (ii), (iii) and (iv) (150mg) shown by nmr to be mainly cis and trans 2,2-bis(trifluoromethyl)-4,5-dichloro-4-fluoro-1,3-dioxolane ((iii) and (iv) by g.l.c.) by comparison with authentic samples, (ii) being tentatively identified by nmr/ms as 2,2-bis(trifluoromethyl)-4,5-dichloro-1,3-dioxolene, [Found: M(Mass Spec) 276. $C_5Cl_2F_6O_2$ requires M(Mass Spec)276], and component (v) (700mg), identified as 2,2-bis(trifluoromethyl)-4,4,5-trichloro-1,3-dioxolane b.p. 132° [Found: C,19.1; H,0.4%; M(Mass Spec)277. $C_5HCl_3F_6O_2$ requires C,19.2; H,0.3%; M-Cl(Mass Spec)277] ^{1}H nmr 6.44δ(s).

Reaction of 2,2-bis(trifluoromethyl)-4/5-difluoro-1,3-dioxolane with $AlCl_3$

The dioxolane (6.2g) was treated with anhydrous $AlCl_3$ as above, and the product (2.7g) vacuum distilled from the reaction mixture. Separation by g.l.c. (15% SE 30, 72-8°, 150cm^3/min He) gave (i) starting material (180mg) (ii) 2,2-bis(trifluoromethyl)-4-chloro-cis-5-fluoro-1,3,-dioxolane (690mg) b.p. 95.5° [Found: C,23.0; H,0.8%; M(Mass Spec)243. $C_5H_2ClF_7O_2$ requires C,22.9; H,0.8%; M-F(Mass Spec)243] ^{1}H nmr 6.35δ(d,-CHF-), 6.30δ (d,-CHCl-), ^{19}F nmr 133.5ppm (from $CFCl_3$)(1F, ddq,-CHF-) (iii) 2,2-bis-(trifluoromethyl)-4/5-dichloro-1,3-dioxolane (1.28g) b.p. 118° [Found: C,21.6; H,0.9%; M(Mass Spec)243. $C_5H_2Cl_2F_6O_2$ requires C,21.5; H,0.7%; M-Cl(Mass Spec)243] ^{1}H nmr 6.46δ(s) ^{19}F nmr 79.0ppm (from $CFCl_3$) and (iv) the cis isomer of (iii)(30mg) with identical nmr/ms but slight differences in the i.r. spectrum. (Cis/trans assigned from i.r. spectra).

Chlorination of 2,2-bis(trifluoromethyl)-1,3-dioxolane

Chlorine gas (127g) was bubbled through the dioxolane (151g) in pyrex glassware irradiated by a medium pressure mercury vapour lamp. A water-cooled condenser led to a dry ice trap so that unreacted chlorine could be recycled. The product (178g) was essentially one compound (g.l.c.), a portion of which was purified (SE 30, 80°, 110cm^3/min He) to give 2,2-bis(trifluoromethyl)-4-chloro-1,3-dioxolane b.p. 114-116° [Found: C,24.4; H,1.4%; M(Mass Spec)175. $C_5H_3ClF_6O_2$ requires C,24.6; H,1.2%; M-CF_3(Mass Spec)175] ^{1}H nmr 6.37δ(1H, dd,-CHCl-), 4.69δ/4.57δ(1H each,-$CH_{ax}H_{eq}$-). A portion (111g) of the product of the first chlorination was further reacted with chlorine (49g) to give a product (160g) of which a portion (1.9cm^3) was separated by g.l.c. (15% SE 30, 100°, 100cm^3/min He) to give (i) 2,2-bis(trifluoromethyl)-4,5-dichloro-1,3-dioxolane (70% by g.l.c.) identified as cis/trans mixture by its i.r. spectrum and (ii) 2,2-bis-(trifluoromethyl)-4,4,5-trichloro-1,3-dioxolane (30% by g.l.c.) identified by its i.r. spectrum. On further chlorination of the product mixture a fourth component was formed (g.l.c.) and was isolated by g.l.c. (15% SE 30, 110°, 120cm^3/min He) to give 2,2-bis(trifluoromethyl)-4,4,5,5-tetrachloro-1,3-dioxolane b.p. >140° [Found: C,16.4; H,0.0%. $C_5Cl_4F_6O_2$ requires C,17.2; H,0.0%]

Fluorination of 2,2-bis(trifluoromethyl)-4,4,5-trichloro-1,3-dioxolane

A mixture (31.8g) of predominantly the trichloro-, but with some dichloro- and tetrachloro, derivatives as prepared above was added dropwise to stirred antimony trifluoride (75g) and antimony pentachloride (5cm^3) at 70°. Distillation gave a product (27g) b.p. 90-100°, a portion (2.75cm^3) of which was separated by g.l.c. (15% SE 30, 75°, 110cm^3/min He) to give (i) 2,2-bis(trifluoromethyl)-4,4-difluoro-5-chloro-1,3-dioxolane (140mg) identified by i.r. spectrum; Mass Spec/nmr showed a trace of 2,2-bis-(trifluoromethyl)-4/5-difluoro-1,3-dioxolane by comparison with an authentic sample; (ii) a mixture (1.2g) which was further separated (15% DEHS, 100°, 120cm^3/min He) to give (iia) 2,2-bis(trifluoromethyl)-4,5-cis-dichloro-4-fluoro-1,3-dioxolane (160mg) [Found: M(Mass Spec)261. $C_5HCl_2F_7O_2$ requires M-Cl(Mass Spec)261] ^{1}H nmr 6.40δ(-CHCl-), ^{19}F nmr 57.28ppm (from $CFCl_3$) (1F, dq,-CFCl-, J_{HF} 7.0 Hz), and (iib) a mixture (95mg) of the trans isomer of (iia) and 2,2-bis(trifluoromethyl)-4-chloro-cis-5-fluoro-1,3-dioxolane identified by i.r./nmr comparison with authentic samples; (iii) the trans isomer of (iia) (1.1g) b.p. 106.5° [Found: C,20.3; H,0.2; Cl,23.5%; M(Mass Spec)261. $C_5HCl_2F_7O_2$ requires C,20.2; H,0.4; Cl,23.9%; M-Cl(Mass Spec)261] ^{1}H nmr 6.47δ(-CHCl-), ^{19}F nmr 48.7ppm (1F, dq,-CFCl-, J_{HF} 8.0 Hz), and (iv) 2,2-bis(trifluoromethyl)-4,4,5-trichloro-5-fluoro-1,3-dioxolane (76mg) by i.r. comparison with an authentic sample.

A second portion (19.0g) of starting material was added dropwise to stirred SbF_3Cl_2 (from 20g SbF_3) at 80° and refluxed for 12hr. Distillation gave a product (14.6g) b.p. 60-80° which was separated by g.l.c. (15% DEHS, 80°, 110cm^3/min He) to give (i) 2,2-bis(trifluoromethyl)-4,4,5-trifluoro-1,3-dioxolane (40% by g.l.c.) identified by i.r. spectrum (ii) 2,2- bis-(trifluoromethyl)-4,5-dichloro-4,5-difluoro-1,3-dioxolane (20% by g.l.c.) shown by nmr/ms/i.r. to be cis/trans (50:50) by comparison with authentic mixture and (iii) 2,2-bis(trifluoromethyl)-4,4-difluoro-5-chloro-1,3-dioxolane (40% by g.l.c.) by i.r. spectrum.

Fluorination of mixed trichloro- and tetrachlorobis(trifluoromethyl) dioxolanes

A 50:50 mixture of the two dioxolanes (63g) was added dropwise to stirred SbF_3Cl_2 (from 55g SbF_3) at 70° and the whole refluxed for 12hr. Distillation gave fraction 1 (16.3g) b.p. 60-80° and fraction 2 (38.1g) b.p. 100-112°. A portion of fraction 1 (1cm^3) was separated by g.l.c. (15% DEHS, 100°, 100cm^3/min He) to give 2,2-bis(trifluoromethyl)-4,5-dichloro-4,5-difluoro-1,3-dioxolane (1.07g) b.p. 80° [Found: C,18.0;

H,0.0%; M(Mass Spec)279. $C_5Cl_2F_8O_2$ requires C,19.1; H,0.0%; M-Cl(Mass Spec)279] ^{19}F nmr 58.5ppm (from $CFCl_3$)(2F, m,-CFClCFCl-, J_{FF} 2.8 Hz, cis isomer), 80.2 and 80.6ppm (3F each,CF_3—+—CF_3, cis isomer), 50.6ppm (from $CFCl_3$)(2F, m,-CFClCFCl-, J_{FF}0 Hz, trans isomer), 80.5ppm (6F,CF_3—+—CF_3, trans isomer), ratio of cis/trans 50:50. Fraction 2 was shown to be a 50:50 mixture of 2,2-bis(trifluoromethyl)-4,4,5-trichloro-5-fluoro-1,3-dioxolane and 2,2-bis(trifluoromethyl)-4,5-dichloro-4,fluoro-1,3-dioxolane by g.l.c. retention times, and was further fluorinated with SbF_3Cl_2 (from 40g SbF_3) at 80° fro 12hr to give 31g product b.p. 70-80°, shown by g.l.c. retention time to be mainly 2,2-bis(trifluoromethyl)-5-chloro-4,4-difluoro-1,3-dioxolane.

The product (31g) was combined with fraction 1 from the first fluorination (approx. 15g) and reduced with hydrogen over palladium at 200° to give 10.8g product (collected in a dry ice trap) which was fractionated to give fraction 1 (3.7g) b.p. 57-60° and a residue (≈7.1g). Fraction 1 (1.5cm^3) was separated by g.l.c. (15% DEHS, 70°) to give (i) 2,2-bis(trifluoromethyl)-4,4,5-trifluoro-1,3-dioxolane (10% by g.l.c.) by i.r. spectrum, (ii) 2,2-bis(trifluoromethyl)-4,4-difluoro-1,3-dioxolane (7% by g.l.c.) [Found: M(Mass Spec)227. $C_2H_2F_8O_2$ requires M-F(Mass Spec) 227] ^1H nmr 4.55δ(-CH_2O-), ^{19}F nmr 75.4ppm (from $CFCl_3$)(2F, tm,-CF_2CH_2-, J_{HF} 9.0 Hz), and (iii) hexafluoroisopropanol (≈100mg) by i.r. spectrum. A sample (1.75cm^3) of the residue was separated by g.l.c. (15% DEHS, 90-110°, 120cm^3/min He) to give mainly (i) 2,2-bis(trifluoromethyl)-4,4-difluoro-5-chloro-1,3-dioxolane, a small amount of (ii) a mixture which was further separated by g.l.c. (15% SE 30, 40°) to give (iia) 2,2-bis(trifluoromethyl)-4/5-difluoro-1,3-dioxolane by i.r. spectrum and (iib) 2,2-bis(trifluoromethyl)-4-chloro-4,5-difluoro-1,3-dioxolane, ^1H nmr 6.14δ (-CHF-) ^{19}F nmr 118.2ppm (from $CFCl_3$)(1F, ddq,-CHF_{ax}-, J_{FF} 1.6 Hz), 58.9ppm (from $CFCl_3$)(1F, dm,-$CF_{ax}Cl$-, J_{HF} 2.0 Hz), and (iii) 2,2-bis(trifluoromethyl) -4,5-cis-difluoro-1,3-dioxolane [Found: M(Mass Spec)227. $C_5H_2F_8O_2$ requires M-F(Mass Spec)227]. ^1H nmr 6.15δ(-CHFCHF-), ^{19}F nmr 139.2ppm (from $CFCl_3$) (2F, dm,-CHFCHF-), 82.36ppm (3F, m,-CF_3), 80.66ppm (3F, m,-CF_3).

Fluorination of tetrachlorobis(trifluoromethyl)dioxolane

The dioxolane (20g) was added dropwise to stirred antimony trifluoride (62g) and antimony pentachloride (4.5cm^3) at 120°, and the product (19.4g) b.p. 60-120° isolated by distillation. A sample (2.7g) was separated by g.l.c. (15% SE 30, 110°, 120cm^3/min He) to give (i) 2,2-bis(trifluoromethyl)

-4,5-dichloro-4,5-difluoro-1,3-dioxolane (250mg) by i.r./nmr/ms (Cis/trans ration 50:50 by nmr), (ii) 2,2-bis(trifluoromethyl)-4,4,5-trichloro-5-fluoro -1,3-dioxolane (1.5g) b.p. 120.5° [Found: C,17.6; H,0.0%; M(Mass Spec)295. $C_5Cl_3F_7O_2$ requires C,18.1; H,0.0%; M-Cl(Mass Spec)295]. ^{19}F nmr 44.2ppm (from $CFCl_3$)(1F, m,-CFClCCl$_2$-) and (iii) starting material (290mg) by i.r. spectrum.

Dehalogenation of dichlorobis(trifluoromethyl)dioxolane

The dichlorocompound (40.2g, with minor amounts of other chloroderivatives) in ether (18cm^3) was added to methanol (18cm^3) and activated zinc dust (10g) at 45°, and refluxed for 1.5hr. Filtration and fractional distillation gave fraction 1 (57-65°), fraction 2 (65°) and a tarry residue. Separation of fraction 1 by g.l.c. (15% SE 30, 75°, 100cm^3/min He) gave a sample tentatively identified as 2,2 bis(trifluoromethyl)-4-chloro-1, 3-dioxolene [Found: M(Mass Spec)242. $C_5HClF_6O_2$ requires M(Mass Spec)242]. ^1H nmr 6.50δ(s,-OCH = CClO).

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 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 [12].

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