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DETAILED INVESTIGATION OF FLUOROMETHYL 1,1,1,3,3,3-HEXAFLUORO-2-PROPYL ETHER (SEVOFLURANE) AND ITS DEGRADATION PRODUCTS.
PART I: SYNTHESIS OF FLUORINATED, SODA LIME INDUCED DEGRADATION PRODUCTS

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SUMMARY

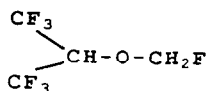
Three fluorinated compounds from the degradation of Sevoflurane (I), fluoromethyl 1,1,3,3,3-pentafluoro-2-propenyl ether (II), fluoromethyl 1-methoxy-1,1,3,3,3-pentafluoro-2-propyl ether (III) and fluoromethyl 1-methoxy-1,3,3,3-tetrafluoro-2-propenyl ether (IV) were synthesized independently and were fully characterized. A side product, fluoromethyl 1-cyano-2,2,2-trifluoroethyl ether (V) was isolated in the synthesis of (II).

INTRODUCTION

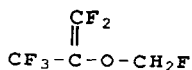
Sevoflurane, fluoromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (I), is a new inhalation anesthetic agent. It could

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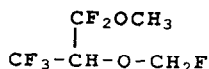
provide rapid induction and recovery in general anesthesia due to its low blood/gas and oil/gas partition coefficients [1]. However, as first reported by Wallin *et al.* [1a], this compound degrades over soda lime, a mixture of calcium oxide, sodium hydroxide and water, under severe laboratory conditions. Two fluorinated products, fluoromethyl 1,1,3,3,3-pentafluoro-2-propenyl ether (II) and fluoromethyl 1-methoxy-1,1,3,3,3-pentafluoro-2-propyl ether (III) resulted from its reactivity over soda lime. After the completion of our current study, Hanaki



(I)

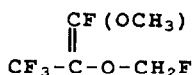


(II)



(III)

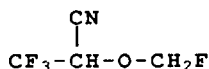
et al. [2] reported on the stability of sevoflurane in an anesthetic circuit (with soda lime) connected to a model lung in a closed system. They found five fluorinated degradation products in which II and III were in appreciable amount whereas in a semi-closed system, II was the major product. All of these products were identified using GLC/MS. In the work of Hanaki *et al.*, no isolation of products was carried out and no synthetic details were reported. Eger *et al.* [3] later did a different stability study based on the loss of sevoflurane with time at various temperatures. They also observed a large fraction of degradation products whose structures were not given. Most recently, Venturella *et al.* [4] studied the sevoflurane stability on dried and wet soda lime in three models: closed, static and a flowing system. Three fluorinated products, (II), (III) and fluoromethyl 1-methoxy-1,3,3,3-tetrafluoro-2-propenyl ether (IV), were found in the static system with dried and commercial soda lime.



(IV)

At present, clinical practice in North America uses soda lime in the breathing circuit to absorb carbon dioxide and to recycle the anesthetic vapor. It is, therefore, necessary to establish the toxicity of degradation products before the anesthetic agent can be used in humans.

Here, we wish to report a useful synthesis of compounds (II), (III) and (IV) [5]. During the preparation of (II), fluoromethyl 1-cyano-2,2,2-trifluoroethyl ether (V) was unexpectedly isolated using an alternative work-up.

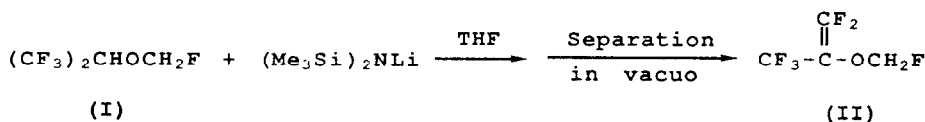


(V)

All of these fluorinated compounds were fully characterized. The synthetic procedure may be scaled-up to prepare large quantities of materials for a full pharmacological study.

SYNTHESIS AND DISCUSSION

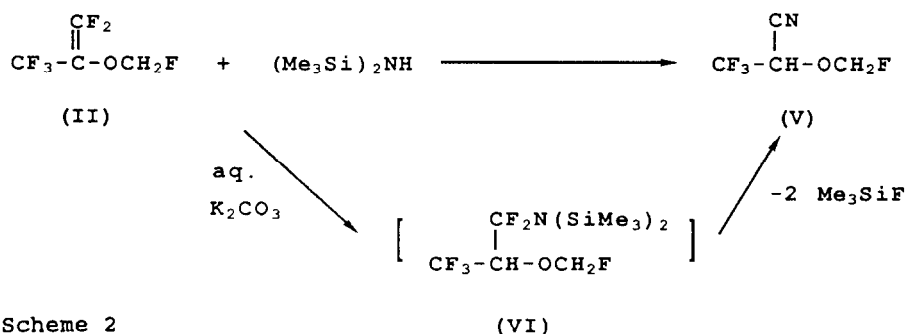
Compound II arises from dehydrofluorination of sevoflurane (I). Bases are usually used to achieve such HF eliminations [6]. In our study, sodium hydride and triethylamine-boron trifluoride complex [7] gave no reaction. However, other bases, in particular, potassium hydroxide, potassium tert-butoxide, sec- and tert-butyl lithium, phenyl lithium and lithium di-isopropylamide gave incomplete reactions with very low yields in the temperature range from -78° to 80°C , while methyl lithium gave complete reaction at -78°C . But in the reaction of sevoflurane with methyl lithium containing diethyl ether, it was difficult to isolate the products by fractional distillation. In addition, this reaction was too violent to scale-up. Finally, we found that lithium bis(trimethylsilyl)amide in THF reacted with sevoflurane very smoothly at -70° to -60°C (Scheme 1) to produce (II) in 50-60% yields. Both product (II) and THF were removed from the



Scheme 1

reaction mixture under anhydrous conditions at reduced pressure and at low temperature. These conditions were necessary to minimize secondary reactions. Product (II) was then isolated by fractional distillation. Compound (II) was characterized by infrared ($-\text{C}=\text{C}-$ stretching at 1764.9 cm^{-1}), ^{19}F and ^{13}C NMR spectroscopies and other analytical techniques. The detailed investigation by ^{19}F and ^{13}C NMR are reported elsewhere [8].

When the reaction mixture was worked-up by adding small amount of aqueous potassium carbonate solution, an exothermic reaction was observed at about 0°C . This reaction produced an unexpected new compound, fluoromethyl 1-cyano-2,2,2-trifluoroethyl ether (V), as the major product. Apparently, (V) resulted from the nucleophilic addition of the co-product, bis(trimethylsilyl)amine, to the double bond of (II). Catalysis by potassium carbonate solution produced an intermediate, (VI), which underwent an unusual β -elimination of two moles of fluorotrimethylsilane (Scheme 2).

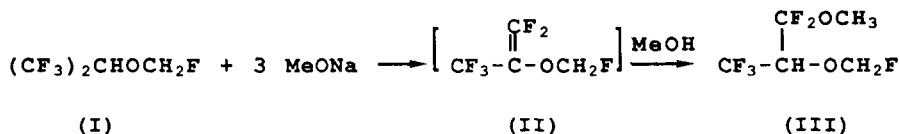


Scheme 2

This elimination is probably driven by the formation of a strong Si-F bond which results in a gas - fluorotrimethylsilane [9]. Fluorotrimethylsilane was isolated by distillation at

16°-18°C (lit. 16°C [10]). A proton coupled ¹⁹F NMR spectrum of this compound shows a quartet at δ-158.4 ppm and J(F,H)=7.6 Hz. It was not possible to observe the intermediate (VI) by GLC and MS methods. Compound (V) showed a triple bond (C≡N) stretching at 2260 cm⁻¹ in the IR. All of the structural analyses agree with (V).

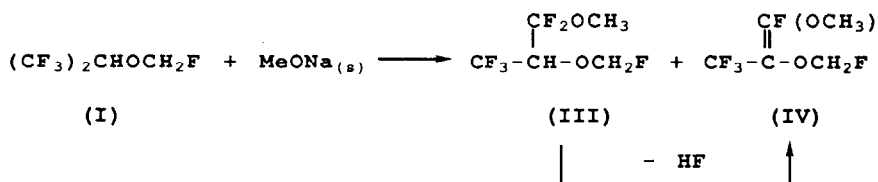
Apparently, the diether (III) occurs from the addition of methanol to (II). Such nucleophilic addition is very common and the reaction product usually undergoes further dehydrofluorination to yield a final olefinic product [11]. Alternately, compound (III) can be synthesized, without the presence of olefinic contaminants, by reacting sevoflurane with sodium methoxide in methanol solution under reflux. The optimum conditions to obtain compound (III) without olefinic contaminants were: addition of 3 moles (25% by weight in methanol) of sodium methoxide to one mole of sevoflurane over 2 1/2 hours. The reaction was under reflux for 2 hours. The reaction afforded compound (III) in 20-30% yields with a small amount of unreacted sevoflurane.



Scheme 3

The reaction scheme 3 is proposed for the formation of the diether (III) in which the olefinic intermediate (II) reacts rapidly with methanol to yield (III). The presence of an intermediate (II) in scheme 3 was detected by GLC during the progress of reaction. Compound (III) was easily isolated by distillation. Complete analytical data of the diether (III) is reported in the Experimental Section.

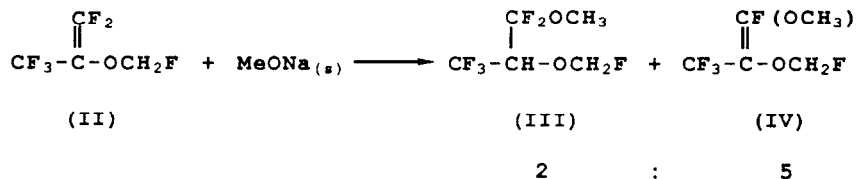
When solid sodium methoxide was added to sevoflurane, the reaction produced about equal amounts of (III) and (IV) (Scheme 4).



Scheme 4

Formation of compound (IV) from (III) by elimination of hydrogen fluoride was also proposed by Hanaki *et al.* [3]. In the present study, it was observed that the reaction yield for (IV) was low and about two thirds of the starting sevoflurane remained unreacted.

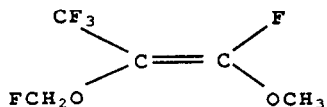
When powdered sodium methoxide reacted with the olefin (II) at 0°C (Scheme 5), both products, (III) and (IV), were formed. According to GLC analysis, the ratio of these products was 2:5. However, when THF was added as a solvent, the yield decreased.



Scheme 5

Unfortunately, because of the same boiling temperature range for compounds (III) and (IV), it was not possible to separate (IV) from (III) by distillation. Therefore, we used preparative GLC to obtain pure (IV) after the preliminary purification of the crude mixture by distillation. The yield obtained by this method was low.

Both IR and high resolution NMR were used to determine the molecular structure of the methoxy olefin (IV). In the IR spectrum, a characteristic, strong stretching band for C=C at 1726.9 cm^{-1} was identified. Compound (IV) can exist in either the Z (CF₃ and F on the same side of double bond) or E (CF₃ and F on opposite side) form. Fluorine coupling constants, between CF₃ and the olefinic F, can be used to distinguish Z and E isomers. The magnitude of fluorine coupling constant for the E isomer is normally larger than the Z isomer [12]. The observed coupling constant between CF₃ and the olefinic F in compound (IV) is 22.2 Hz. This suggests that the methoxy olefin (IV) is in the Z form.



(IV), Z form

NMR data also suggest the presence of impurities in small traces (<1%). No attempts were made here to determine their structures.

EXPERIMENTAL

GLC analyses were carried out on a HP 5790 Gas Chromatograph equipped with a thermal conductivity detector. The columns used were stainless steel 1/8" x 10' of 5% OV-17, 5% SE-30, 10% Carbowax 20 M or 1/8" x 20' of 10% Igepal CO-880/15% Ucon LB-550X. Preparative GLC separation was performed on a Vorex 1040 Gas Chromatograph with thermal conductivity detector using two 1 cm x 1 m stainless steel, 10% OV-17 columns connected together. Helium was the carrier gas in all cases.

Mass spectra by electron impact (EI) technique were obtained from a HP 5995B Gas Chromatograph/Mass Spectrometer using an electron beam energy of 70 eV. Spectra obtained by chemical ionization (CI) technique were collected on a similar instrument with variable electron beam energy*. The GLC column used was 10% Carbowax 20M WCOT.

* Courtesy of Rutgers University, New Brunswick, New Jersey (U.S.A.)

High resolution NMR spectra were obtained on an IBM AF 270 Fourier Transform Spectrometer. ^1H (270.13 MHz) and ^{13}C (67.9 MHz) NMR chemical shifts were recorded relative to tetramethylsilane. ^{19}F (254.17 MHz) NMR chemical shifts were recorded relative to fluorotrichloromethane with negative values assigned to signals at higher field and positive values assigned to signals at lower field. ^1H (270.13 MHz), ^{13}C (67.9 MHz) and ^{19}F (254.17 MHz) NMR data of compounds (II), (III), (IV) and (V) are listed in Tables 1, 2, and 3 respectively.

Infrared spectra were obtained on a Digilab FTS-60 Spectrometer.

Elemental analyses were performed by Robertson Laboratories, Madison, New Jersey.

Fluoromethyl 1,1,3,3,3-pentafluoro-2-propenyl ether (II)

To a solution of 60.1 g (0.30 mole) of sevoflurane in 40 ml of dried THF, 330 ml (0.33 mole) of a 1.0 M solution of lithium bis(trimethylsilyl)amide in THF was added at -70°C under N_2 . The addition was completed in 55 minutes and the reaction mixture was stirred at -70°C for another 15 minutes. Sevoflurane was consumed completely as indicated by GLC. The mixture was stored at -20°C overnight. Pot to pot distillation of the mixture at -40° to -20°C and 5 mm to 2 mm Hg gave 228.6 g of a colorless liquid which contained 12.4% of (II) (GLC analysis). Fractional distillation of this liquid at atmospheric pressure provided 8 fractions (total weight of 33.9g) containing concentration of (II) varying from 74.4% to 99.0%. The yield based on GLC data of the distillates was 56.5% (30.5g). The fraction with 99.0% (II) was collected at 46° - 47°C . A distillate of 6.7 g at 97.9% purity was further purified by Preparative GLC to afford 4.5 g of 99.9% pure II. MS(EI): M/z 180 (M^+), 69 (CF_3^+ , base peak); (CI): M/z 180 (M^+), 161 (M^+-F , base peak). IR: 1764.9 cm^{-1} (C=C). Elemental analysis for $\text{C}_4\text{H}_2\text{F}_6\text{O}$: calc'd C 26.68%, H 1.11%, F 63.31%. Found C 26.53%, H 1.09%, F 63.01%.

Fluoromethyl 1-cyano-2,2,2-trifluoroethyl ether (V)

Lithium bis(trimethylsilyl)amide (1.0 M) in THF, 850 ml (0.85 mole), was added over 30 minutes to a solution of 160.0 g (0.80 mole) of sevoflurane in 120 ml of dried THF at -65°C under N_2 . The reaction mixture was stirred for another 30 minutes at the same temperature. A 10% potassium carbonate solution, 9 ml, was added at -60°C and the dry ice-acetone bath was replaced by an ice water bath. An exothermic reaction occurred when the temperature of the reaction mixture reached about 0°C . After the exothermic activity subsided, the reaction mixture was filtered and the liquid was distilled at atmospheric pressure. Two fractions collected at $16^{\circ}\text{--}18^{\circ}\text{C}$ (lit. 16° [10]) had a total liquid weight of 85.6 g and were found to be Me_3SiF with purity 99.7-99.9%. Another fraction collected at $20^{\circ}\text{--}65^{\circ}\text{C}$, weight 28.5 g, was a mixture of Me_3SiF , compound (II) (32.2% by GLC) and THF. Yield of (II) based on GLC was 6.4%. The distillation residue had a weight of 934.7 g which contained about 7.0% of compound (V).

Another similar run starting with 78.4 g (0.39 mole) of sevoflurane was conducted and resulted in a residue of 456.2 g containing about 6.7% of (V) after the first distillation.

The above two residues were mixed together and the mixture was re-distilled at atmospheric pressure. A liquid, 45.5 g, collected at $111^{\circ}\text{--}112.5^{\circ}\text{C}$ had a purity of (V) over 99.7%. MS(EI): m/z 156($\text{M}^+\text{-H}$), 138($\text{M}^+\text{-F}$), 33 (FCH_2^+ , base peak). IR: 2260 cm^{-1} ($\text{C}\equiv\text{N}$). Elemental analysis for $\text{C}_4\text{H}_3\text{F}_4\text{NO}$: calc'd C 30.58%, H 1.92%, F 48.38%, N 8.92%. Found C 30.26%, H 1.92%, F 48.06%, N 8.94%.

Fluoromethyl 1-methoxy-1,1,3,3,3-pentafluoro-2-propyl ether (III)

To 20.0 g (0.1 mole) of sevoflurane was added 64.8 g (0.3 mole) of 25% by weight of sodium methoxide in methanol at $15^{\circ}\text{--}22^{\circ}\text{C}$ over 45 minutes under N_2 . After this reaction mixture was stirred at room temperature for 1 3/4 hours more and was then heated to reflux for an additional 2 hours. The mixture was then cooled and was poured into 400 ml of ice water. The organic liquid was washed with water and saturated NaCl solution. Finally, the liquid was dried at -20°C overnight to give 15.9 g of crude product which contained 5.0% sevoflurane

and 57.6% of (III) by GLC analysis. The crude product was distilled at 55°-57°C, 70 mm Hg to give 4.9 g of over 98% pure (III). This corresponds to 23% yield. The distillate was treated with molecular sieves 5A to remove methanol contaminant to give a purity of liquid over 99.8%. MS(EI): M/z 193 (M⁺-F), 81(CH₃OCF₂⁺, base peak). Elemental analysis for C₅H₆F₆O₂: calc'd C 28.31%, H 2.85%, F 53.74%. Found C 28.05%, H 2.75%, F 53.55%.

Fluoromethyl 1-methoxy-1,2,2,2-tetrafluoro-2-propenyl ether (IV)

Method 1

Powdered sodium methoxide, 20.3 g (0.375 mole), was added over a period of 3 1/4 hours to 40.1 g (0.201 mole) of sevoflurane at 23°-41°C under N₂. The reaction mixture was stirred at 35°-40°C for another 30 minutes and cooled to 0°C. Ice cold water, 100 ml, was added to the mixture slowly. The organic liquid was separated, then washed with water and dried at -20°C overnight to give 22.6 g of liquid which contained 64.2% of sevoflurane, 11.4% of compound (III) and 15.3% of desired compound (IV) (GLC analysis). Distillation of this liquid at 44-47°C, 42 mm Hg gave 4.2 g of a mixture of III and IV. Preparative GLC separation of 2.474 g of the mixture afforded 0.375 g relatively pure (IV). MS(EI): m/z 192(M⁺), 173 (M⁺-F), 69 (CF₃⁺, base peak). IR: 1726.9 cm⁻¹ (C=C). Elemental analysis for C₅H₅F₅O₂: calc'd C 31.26%, H 2.62%, F 49.45%. Found C 30.86%, H 2.70%, F 49.65%.

Method 2

Powdered sodium methoxide, 1.91 g (0.0354 mole), was added over 35 minutes to 3.62 g (0.0197 mole) of (II) at 0°-10°C. The reaction mixture was stirred at 0°C for another hour and 15 ml of water was gradually added. The organic liquid was separated, washed with water and saturated NaCl solution to give 2.67 g of crude product mixture which contained 6.1% of (II), 22.5% of (III) and 59.5% of (IV) (GLC analysis). Another similar reaction was started with 3.7 g (0.0206 mole) of (II) and 1.67 g (0.0309 mole) of sodium methoxide (solid). This

afforded 3.34 g of similar product mixture. The above two crude product mixtures were combined together and distilled at 40°-50°C, 60 mm Hg to give 2.96 g of a mixture of (III) and (IV) (64%). Preparative GLC separation of 1.2 g of this mixture gave 0.175 g of >95% pure (IV).

TABLE 1

¹H NMR Data

Structure	Chemical Shift ppm	Coupling Constant Hz
$\begin{array}{c} \text{CF}_2 \\ \\ \text{CF}_3\text{-C-OCH}_2\text{F} \end{array}$	5.5 (d)	J(HCF)=53.0
$\begin{array}{c} \text{CF}_2\text{OCH}_3 \text{ } a \\ \\ \text{CF}_3\text{-CH-OCH}_2\text{F} \\ \text{ } b \quad c \end{array}$	a 3.7 (s) b 4.3 (m) c 5.4 (d)	J(HCF)=56.0
$\begin{array}{c} \text{CF(OCH}_3) \\ \\ \text{CF}_3\text{-C-OCH}_2\text{F} \\ \text{ } b \end{array}$	a 3.9 (s) b 5.4 (d)	J(HCF)=53.5
$\begin{array}{c} \text{CN} \\ \\ \text{CF}_3\text{-CH-OCH}_2\text{F} \\ \text{ } a \quad b \end{array}$	a 4.9 (q) b 5.5 (d of q)	J(HCCF)=5.3 J(HCF)=53.0 J(HCOCCF)=3.2

CONCLUSION

We have presented a successful synthesis of three fluorinated, soda lime induced, degradation products found in our stability study by reacting sevoflurane or (II) with commercially available reagents. The isolation of an unexpected side product, (V), was also described. All of these compounds were characterized by various analytical methods, especially using NMR and IR, and the structures of (II), (III), and (IV) agree with those proposed by Hanaki *et al.* [3].

TABLE 2

 ^{13}C NMR Data (broad band decoupled)

Structure	Chemical Shift ppm	Coupling Constant Hz
$\begin{array}{c} d \text{ CF}_2 \\ \\ \text{CF}_3\text{-C-OCH}_2\text{F} \\ c \quad b \quad a \end{array}$	<i>a</i> 103.8 (d of t)	$J(\text{CF})=229,$ $J(\text{COC}=\text{CF})=3.5$
	<i>b</i> 109.3 (m)	
	<i>c</i> 120.7 (t of q)	$J(\text{CF})=271,$ $J(\text{CC}=\text{CF})=5.5$
	<i>d</i> 157.5 (t)	$J(\text{CF})=299$
$\begin{array}{c} \quad \quad \quad a \\ d \text{ CF}_2\text{OCH}_3 \\ \\ \text{CF}_3\text{-CH-OCH}_2\text{F} \\ e \quad b \quad c \end{array}$	<i>a</i> 50.7 (t)	$J(\text{COCF})=7.5$
	<i>b</i> 75.6 (m)	
	<i>c</i> 103.0 (d)	$J(\text{CF})=224.1$
	<i>d</i> 120.3 (t)	$J(\text{CF})=264.7$
	<i>e</i> 121.5 (q)	$J(\text{CF})=282.0$
$\begin{array}{c} \quad \quad \quad a \\ e \text{ CF}(\text{OCH}_3) \\ \\ \text{CF}_3\text{-C-OCH}_2\text{F} \\ d \quad c \quad b \end{array}$	<i>a</i> 57.7 (d)	$J(\text{COCF})=7.0$
	<i>b</i> 104.1 (d)	$J(\text{CF})=225.8$
	<i>c</i> 110.9 (m)	
	<i>d</i> 121.8 (d of q)	$J(\text{CF})=270.5,$ $J(\text{CC}=\text{CF})=6.4$
	<i>e</i> 158.1 (d)	$J(\text{CF})=291.6$
$\begin{array}{c} \quad \quad \quad a \\ c \text{ CN} \\ \\ \text{CF}_3\text{-CH-OCH}_2\text{F} \\ d \quad a \quad b \end{array}$	<i>a</i> 65.8 (q)	$J(\text{CCF})=38.5$
	<i>b</i> 101.5 (d)	$J(\text{CF})=226.2$
	<i>c</i> 110.6 (s)	
	<i>d</i> 120.2 (q)	$J(\text{CF})=281.6$

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