Practical preparation of some potentially anesthetic fluoroalkanes: regiocontrolled introduction of hydrogen atoms

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(Received July 26, 1991; accepted March 31, 1992)

Abstract

Methods are described for the large-scale preparation of a number of fluoroalkanes, which have been tested for general anesthesia.

Introduction

Diverse gaseous and volatile compounds produce general anesthesia. These include alkanes (e.g. chloroform, cyclopropane or halothane), ethers (e.g. diethyl ether), the modern halogenated ethers (e.g. enflurane or isoflurane), nitrous oxide and more exotic compounds (e.g. xenon, carbon tetrafluoride and sulfur hexafluoride.) Although our catalog of such compounds has led to observations on structure–activity relationships in anesthesia [1, 2], a more definitive view might result from a knowledge of the properties of a continuous, parallel series. Figure 1 shows some of the alkanes that were deemed necessary to test the theory of selective hydrogen atom placement within the molecule. The development of such a series would permit a determination of the impact of molecular size, halogenation (particularly fluorination), the placement of halogens on anesthetic potency and other variables. Some of the compounds needed for such a series were immediately available; others, however were not. The present report describes the synthesis of the latter compounds.

Experimental

NMR spectra were recorded on a 270 MHz Bruker spectrometer; ^{1}H NMR spectra were referenced to internal tetramethylsilane ($\delta = 0$); ^{19}F NMR

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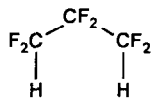
0022-1139/92/$5.00

C_3



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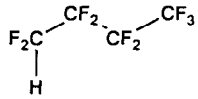

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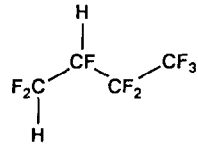

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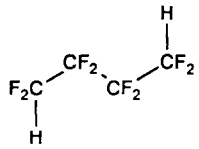

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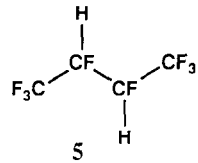

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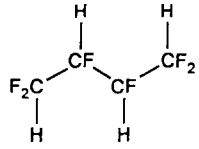

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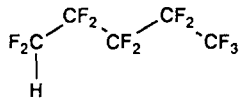

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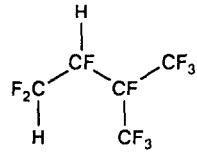

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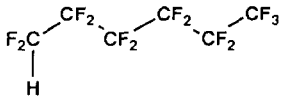
C_6



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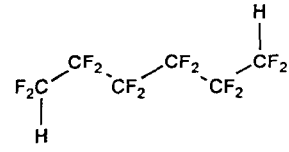

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Fig. 1.

spectra were obtained at 188 MHz; the external reference was $CFCl_3$ ($\delta = 0$); the internal reference used was hexafluorobenzene ($\delta = -163.0$). The column used for GC was a 50 m$\times$0.2 mm$\times$0.5 μm, SE30 silica capillary column.

1H, 3H-perfluoropropane (1) [3]

Hexafluoroglutaric acid (140 g) was dissolved in 150 ml absolute ethanol and titrated with 30% aqueous NaOH. The solvent was removed *in vacuo*

at 80–100 °C, and the resulting sodium salt was recrystallized from ethanol/water (4:1) to yield 111.5 g white crystals. An additional 53.2 g was obtained in two batches from the mother liquor for a total yield of 99%. The salt (111 g), dried thoroughly *in vacuo*, was heated in 280 ml ethylene glycol to 280 °C (temperature of oil bath) over 9 h. The gaseous product (54.1 g, 91%) was passed through aqueous NaOH, then Drierite, and collected at −78 °C. The purity was shown to be >99.6% by GC. ^{1}H NMR $CDCl_3$ δ: 5.94 (tm, J=52 Hz, J=4.5 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −136.0 (s, CF_2); −139.5 (d, CF_2H, J=52 Hz) ppm.

1H-perfluorobutane (2) [4–6]

1-Iodoperfluorobutane (100 g, 0.29 mol) was added dropwise to a warm mixture of zinc dust (28.4 g, 0.43 mol) and a catalytic amount of zinc chloride in methanol. The mixture was refluxed for 0.5 h, and the product was collected with a dry-ice condenser. It was further purified by spinning-band distillation to yield 46 g (72%) product, shown to be >99.5% pure by GC. B.p., 14 °C. ^{1}H NMR $CDCl_3$ δ: 6.03 (tt, J=52 Hz, J=5.0 Hz) ppm.

1H, 2H-perfluorobutane (3) [6]

Perfluoropentanoic acid (75 g, 0.28 mol) was dissolved in 50 ml water; the solution was brought to pH 6 with NaOH. The resulting sodium salt was dried, then heated to 300 °C. The gaseous product was passed through 30% aqueous KOH, then Drierite, and condensed at −78 °C to yield 55.1 g (98% yield) perfluoro-1-butene. A column packed with 1% palladium on alumina and heated to 70 °C was flushed with argon then hydrogen, and the perfluoro-1-butene (kept at −7 °C to −9 °C) was slowly evaporated by means of a stream of hydrogen and passed through the column. The product (52.3 g, 94%) was collected at −78 °C. B.p., 34.5 °C. ^{1}H NMR $CDCl_3$ δ: 6.04 (tdd, (J=53 Hz, J=6.4 Hz, J=4.3 Hz), 1H); 4.98 (dm, J=59 Hz, 1H) ppm. ^{19}F NMR δ: −84.6; −126.4; −131.6; −219.2 ppm.

1H, 4H-perfluorobutane (4) [6, 7]

Octafluoroadipic acid (5.0 g, 0.017 mol) in 5 g water was neutralized with 25% aqueous KOH to a phenolphthalein endpoint. The resulting salt, dried in a high vacuum, was decarboxylated in 25 ml refluxing ethylene glycol for 5 h to yield, after distillation, 3.1 g (89%) of product, which was further purified by spinning-band distillation. B.p., 43 °C. ^{1}H NMR $CDCl_3$ δ: 6.03 (tm, J=52 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −141.4 (d, J=52 Hz): −134.9 ppm.

2H, 3H-perfluorobutane (5) [6, 8]

Condensed perfluoro-2-butene (55.9 g, 0.28 mol) at −5 °C was evaporated by a stream of hydrogen and passed through a heated column (70 °C, 30×1 cm) packed with 15 g 1% palladium on alumina. The product (56.2 g, 99%) was condensed at −78 °C, then further purified by spinning-band distillation. B.p. (mixture of diastereomers), 28–35 °C; (pure diastereomer), 33.5–

33.9 °C. ^{1}H NMR $CDCl_3$ δ: 5.00 (m) ppm. ^{19}F NMR $CDCl_3$ δ: −78.0; −221.1 ppm.

*1,1,2,3,4,4-Hexafluorobutane (**6**) [6, 9]*

Condensed hexafluoro-1,3-butadiene (100 g, 0.62 mol) was slowly evaporated by means of a stream of hydrogen and passed through a heated column (80 °C, 30×1 cm) packed with 1% palladium on alumina. The product was collected at −78 °C and was purified by two spinning-band distillations. Fraction A (11.4 g, 11%): b.p., 61–63.2 °C. ^{1}H NMR $CDCl_3$ δ: 4.75 (m, 2H); 6.02 (tm, 2H, J=54 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −132.1 (d, J=55 Hz); −220.5 (m) ppm. Fraction B (20.1 g, 19%): b.p., 67–68.2 °C. ^{1}H NMR $CDCl_3$ δ: 4.84 (m, 2H); 6.00 (tm, 2H, J=54 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −132.8 (m); −216.5 (m) ppm.

*1H-perfluoropentane (**7**) [5b, 10]*

Undecafluorhexanoic acid (99 g) was dissolved in 50 ml deionized water, then titrated with 30% aqueous NaOH. The solvent was removed *in vacuo* over 48 h to give 99 g (94%) of the sodium salt, which was decarboxylated in ethylene glycol at 195–230 °C. The product (71.8 g, 90%) was condensed in a dry-ice trap and was shown to be 97% pure by GC. The product was further purified by spinning-band distillation. B.p., 44 °C. ^{1}H NMR $CDCl_3$ δ: 6.02 (tt, J=52 Hz, J=5.1 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −138.0; −130.4; − 127.2; −125.1; −81.9 ppm.

*2-Trifluoromethyl-1,1,1,2,3,4,4-heptafluorobutane (**8**) [11]*

Decafluoro-3-methyl-1-butene [14] (68 g, 0.27 mol) was slowly evaporated by means of a stream of hydrogen and passed through a heated column (70 °C, 30×1 cm) packed with 1% palladium on alumina. The product was collected at −78 °C and was purified by spinning-band distillation to yield 53.1 g material (77%). B.p., 49.1–49.6 °C. ^{1}H NMR $CDCl_3$ δ: 5.01 (1H, dm, J=44 Hz); 6.12 (1H, tt, J=53 Hz, J=5.3 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −73.67; −73.18; −128.16; −189.30; −215.83 ppm.

*1H-perfluorohexane (**9**) [5b, 5c]*

1-Iodoperfluorohexane (79 g, 0.20 mol), 30 g zinc dust and 200 ml ethylene glycol were heated at reflux overnight. The product (33 g, 52%) was distilled through a 6 in. Vigreux column packed with glass helices. B.p., 69–70 °C. ^{1}H NMR $CDCl_3$ δ: 6.06 (tt, J 45 Hz, J=5.4 Hz) ppm. ^{19}F NMR $CDCl_3$ δ: −82.6; −124.6; −125.2; −127.9; −131.0; −138.8 (J=53 Hz) ppm.

*7H-dodecafluoroheptanoic acid (**11**)*

1*H*, 1*H*, 7*H*-Dodecafluoro-1-heptanol (100 g) in 220 ml H_2O was treated with potassium dichromate (87 g) and concentrated H_2SO_4 (104 ml) and heated at reflux for 3–4 h. The product was extracted (6×60 ml) with ether. The combined extract was washed with brine, then dried over Na_2SO_4. The

solvent was removed, and the product was distilled *in vacuo* twice to yield 80.5 g (77%) of material that solidified on standing at room temperature. ^{1}H NMR $CDCl_3$ δ: 6.05 (tt, 1H); 7.72 (s, 1H) ppm. ^{19}F NMR $CDCl_3$ δ: −120.4; −123.1; −124.1; −124.7; −130.7; −138.4 (dm, J=56 Hz) ppm.

*1H, 6H-perfluorohexane (**10**) [7]*

7H-Dodecafluoroheptanoic acid (79 g) was dissolved in 70 ml ethanol, then titrated with 40% aqueous NaOH. The solvent was removed *in vacuo*, and the dry sodium salt was heated in 150 ml ethylene glycol up to 240 °C (temperature of oil bath). The distillate was washed with H_2O then filtered through a column packed with Na_2SO_4. The product (57.8 g, 86%) was further purified by spinning-band distillation. B.p., 89 °C. ^{1}H NMR $CDCl_3$ δ: 6.05 (tt) ppm. ^{19}F NMR $CDCl_3$ δ: −124.6; −130.5; −138.1 (d) ppm. Analysis: Calc. for $C_6H_2F_{12}$: C, 23.84; H, 0.66%. Found: C, 23.69; H, 0.67%.

Results and discussion

The introduction of hydrogen into perfluoroalkanes can best be accomplished by either decarboxylation of acid salts in a protic medium, replacement of iodides via zinc reduction or hydrogenation of olefins, themselves being obtained by decarboxylation of acid salts in an aprotic medium. The mono- or di-carboxylic acids required for the preparation of **1**, **4**, **7** and **10** (commercially available or prepared from the corresponding alcohol, **11**) were converted to the sodium or potassium salts and the anhydrous salts decarboxylated by heating in ethylene glycol [4]. 1-Iodoperfluorobutane and 1-iodoperfluorohexane were reduced with zinc dust [10] to furnish **2** and **9**, respectively. Compounds **3**, **5**, **6** and **8** were prepared by high-temperature hydrogenation of the corresponding alkenes over palladium on alumina [12].

Although methods for the synthesis of compounds **1–10** are described in the literature, none was found to be amenable to large-scale preparation, as they are reported to produce either mixtures or low yields. Some of the starting materials reported are not readily available. In other cases, the known compounds were only identified as reaction by-products. The above experimental information reports adjustments in procedures that yield the desired compounds in good to excellent yields.

In each case the final products were purified by spinning-band distillation. (Two compounds, **5** and **6**, were obtained as a mixture of diastereomers, which were separated by spinning-band distillation; however, the exact assignment for the *threo* and *erythro* isomers has not been made, although the pure compounds were characterized.) All the preparations proved practical and were carried out to yield 50–75 g of the final product.

Preliminary test of the anesthetizing properties of these compounds indicate that the addition of hydrogen and an increase in the chain length tend to increase the potencies of these compounds. This is consistent with the work of others in this field. For example, it is known that both 1*H*, 3*H*-

perfluoropropane and 1*H*, 4*H*-perfluorobutane are anesthetic, but the former compound has about one-third the potency of the latter [3]. Similarly, 1*H*-perfluoroethane is not an anesthetic at 1 atm pressure [13], but 1*H*, 1*H*-perfluoroethane provides anesthesia at 0.4 atm pressure [14]. Details of the results of these studies will be provided elsewhere at a later date.

Acknowledgment

The authors are indebted to the Anesthesia Research Foundation (UCSF) for support of this work.

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