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Synthesis and toxicity of 1,2-bis(trifluoromethoxy)-1,1,3,3,3-pentafluoropropane

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Abstract

Recent studies have demonstrated that monofluorination of the methoxy group of the diether fluoromethyl 1-methoxy-1,1,3,3,3-pentafluoro-2-propyl ether yields a compound exhibiting sedative/hypnotic properties. In this study an additional fluorinated analog of this parent compound was synthesized, using photochlorination followed by reaction with bromine trifluoride. In this manner, both methoxy groups were converted to trifluoromethoxy moieties, forming 1,2-bis(trifluoromethoxy)-1,1,3,3,3-pentafluoropropane. This volatile product exhibited no anesthetic effects and was found to be highly toxic in the rat, following both iv infusion and exposure to the vapor.

Keywords: Fluorination; Bromine trifluoride; Fluorinated ether; Fluoroether toxicity; Bromine trifluoride

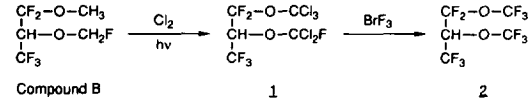
1. Introduction

Bromine trifluoride, BrF_3, is a potent fluorinating agent capable of introducing fluorine into a variety of compounds, such as carboxylic acids [1,2], nitriles and ketones [3]. It has also been used to selectively replace certain aliphatic bromine [4,5], chlorine [6] and hydrogen atoms [7] with fluorine. One area in which BrF_3 has found application is in the synthesis of anesthetics, including the polyfluorinated ethers desflurane [8] and sevoflurane [9,10]. In the case of several methyl ethers, BrF_3 has been found to directly fluorinate the methoxy carbon in one step [7,9–11]. Fluorination of low molecular weight compounds often improves their volatility and provides high chemical and metabolic stability, important attributes of anesthetics.

While the synthetic utility of BrF_3 as a fluorinating agent is clear, the design of new fluorinated compounds with desirable clinical properties remains problematic. Although the broad structural parameters defining the volatile anesthetics are known [12–14], it remains difficult to predict the effect of novel polyhalogenated compounds on the central nervous system (CNS). For example, the modern anesthetics include compounds containing methoxy, fluoromethoxy and difluoromethoxy moieties [1]. Short-chain polyfluorinated compounds may exhibit gross CNS activities ranging from inertness to anesthetic, sedative or convulsant effects [12,13,15,16].

Most of the volatile anesthetics in use today are polyhalogenated monoethers. Recent studies have determined that a polyfluorinated diether, 1,2-bis(fluoromethoxy)-1,1,3,3,3-pentafluoropropane (BFPP), is a hypnotic/sedative in the rat when given intravenously [11]. This compound is too non-volatile (b.p. 141 °C at 1 atm), however, to serve as an inhalational agent. BFPP is derived from fluoromethyl 1-methoxy-1,1,3,3,3-pentafluoro-2-propyl ether (referred to as compound B [17,18]; Scheme 1), which also possesses distinct, though weaker, sedative/hypnotic properties. The pharmacological profile of other fluorinated compound B derivatives remains unknown.

The direct reaction of compound B with BrF_3 results in the substitution of a single methoxy hydrogen with fluorine, thus providing an efficient route to BFPP [11]. This study sought to obtain an additional fluorinated derivative of compound B. This was attempted by chlorinating compound B and reacting the chlorinated intermediate with BrF_3. Several catalysts have been reported to enhance BrF_3 replacement of aliphatic chlo-



Scheme 1. Two-step reaction sequence for the conversion of compound B to **2**.

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rines, and a secondary interest was evaluating the influence of antimony trifluoride (SbF_3) on the course of the reaction [6,9]. Introduction of additional fluorines into BFPP had the potential to yield a compound of higher volatility as well as increased metabolic stability [11]. Herein we report on the successful use of chlorination and BrF_3 to generate a new fluorinated analog of compound B and its effects when administered to rats.

2. Experimental details

2.1. Chemicals

Chlorine was purchased from Air Products Co. Bromine trifluoride (98%) was obtained from Ozark-Mahoning, Inc. (Tulsa, OK) and was transferred to a Teflon storage container prior to use. Antimony trifluoride (99.8%) was from Aldrich Chemical Co. (Milwaukee, WI). Compound B was synthesized from sevoflurane using the literature procedure of Huang et al. [19]. All other chemicals were of reagent grade or higher.

2.2. Instrumentation

A Hewlett-Packard 5890 gas chromatograph equipped with a flame ionization detector was used for GLC analyses. A Restek Rtx-1301 crossbond 6% cyanopropylphenyl/94% dimethylpolysiloxane column (30 m×0.25 mm i.d.) was used. Helium was the carrier gas, with a flow rate of 2 ml min^{-1}. An oven temperature program was employed, with an initial temperature of 30 °C held for 5 min and then increased to 150 °C at 15 °C min^{-1}. Injector and detector temperatures were 170 °C and 250 °C, respectively. A Bruker AC-300 spectrometer was used to obtain ^1H (300.17 MHz), ^{19}F (282.44 MHz) and ^{13}C (75.48 MHz) nuclear magnetic resonance spectra. Samples contained $CDCl_3$ as solvent and, as internal standard, TMS (for ^1H and ^{13}C) or $CFCl_3$ (for ^{19}F). All chemical shifts are reported in parts per million downfield (positive) of the standard. Gas chromatographic–mass spectral data were collected using a Hewlett-Packard 5970 mass spectrometer operated in the electron impact mode. Sample introduction was via the Restek Rtx-1301 column.

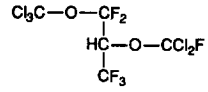
2.3. Photochemical chlorination of compound B

Compound B (3.0 g, 14.1 mmol) was placed in a 25 ml glass test tube along with a magnetic stir bar. The tube was outfitted with a Dry Ice condenser through which was threaded a 3 mm i.d. Teflon transfer line from a cylinder of chlorine. The line terminated just below the surface of compound B.

With compound B being stirred and illuminated by a 250 W incandescent light bulb, dry chlorine gas was bubbled into the test tube. Initially, the yellow color imparted by the chlorine was dissipated rapidly. Over the course of 6 h, chlorine was bubbled in as needed so as to maintain a distinctly yellow solution. Chlorine gas efficiently condensed on the Dry Ice condenser, returning to the solution and reducing the need to add additional gas, especially during the latter stages of the reaction. This also had the effect of cooling the reaction solution, which was periodically warmed using a 40 °C water bath.

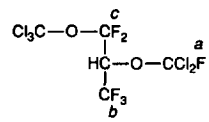
Table 1
NMR data for dichlorofluoromethoxy 1-trichloromethoxy-1,1,3,3,3-pentafluoro-2-propyl ether (1)

^1H NMR data



	Chemical shift (ppm)	Coupling constant (Hz)
	4.92 sextet)	$^3J_{HF}=5.53$

^{19}F NMR data



Fluorine	Chemical shift (ppm)	Coupling constant (Hz)
a	−8.8 (d, 1F)	$^4J_{FH}=6.2$
b	−71.8 (s, 3F)	
c	−77.4 to −78.5 (AB pattern, 2F)	$^2J_{FF}=163$

The crude product was shaken with aqueous 10% sodium carbonate until gas evolution had subsided and then washed with distilled water. GC analysis revealed the product to be approximately 96% pure. Higher purity was achieved by vacuum distillation (78 °C/750 mmHg vacuum) using a Vigreux column, following collection of a small initial fraction. GC–MS and ^1H and ^{19}F NMR analyses revealed the final product to be dichlorofluoromethoxy 1-trichloromethoxy-1,1,3,3,3-pentafluoro-2-propyl ether (**1**), a slightly viscous (density 1.7 g ml^{-1}), colorless liquid which was obtained in 92% yield and >98% purity. The NMR results are summarized in Table 1. Key mass spectral fragments included: *m/z* (EI) 249/251/253 (1:0.6:0.05; $M^+ - OCCl_3$); 167/169 (1.0:0.3; $CF_3CHClCF_2^+$, base peak); 117/119/121 (1.0:0.9:0.28; CCl_3^+); 101/103/105 (1.0:0.52:0.07; CCl_2F^+); 69 (CF_3^+).

2.4. Fluorination of chlorinated compound B (1)

Chlorinated compound B (**1**, 1.1 ml) was placed in a 25 ml round-bottom Pyrex flask containing a side port. A Teflon-coated magnetic spin bar was added. When desired, 8–10 mg of SbF_3 (approx. 50 μmol) was also added. The side port was sealed with a Teflon-wrapped flange septum. Bromine trifluoride was added via a 1 mm i.d. tube inserted through the septum and terminating above the liquid. The tube was connected to a custom Teflon syringe, which permitted BrF_3 to be withdrawn from its storage container and then directed into the flask by use of a three-way valve. The neck of the flask was sealed with a second Teflon-wrapped septum, through which was inserted a 10-in segment of 5 mm i.d. Teflon tubing. The segment passed through the center of the bottom of a plastic beaker, which could be filled with Dry

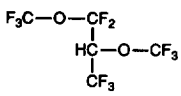
Ice/isopropanol or ice water so as to have the tube segment serve as a condenser. The segment was connected to a glass trap sealable with two Teflon valves, which was immersed continuously in a Dry Ice/isopropanol bath.

With the condenser cooled with Dry Ice/isopropanol and the reaction flask immersed in an ice water bath, BrF_3 (0.8 ml, 16.9 mmol) was cautiously added to the chlorinated material in 100 μl aliquots over a 3-h period. Following the last addition of BrF_3, the trap contents (approximately 0.6 ml of a two-phase mixture of a colorless upper layer and a maroon lower layer) were returned to the reaction flask and two additional 100 μl aliquots of BrF_3 were added. The mixture was allowed to stir an additional 2 h (when SbF_3 was used) or 4–5 h (no catalyst) at ambient temperature, after which the coolant in the condenser flask was changed to ice water. Using a water bath, the reaction mixture was warmed for 20 min to 40 °C, and, by inserting a needle through the side port septum, a gentle stream of nitrogen was briefly passed through the system to force uncollected product into the trap.

With one valve slightly open, the trap was allowed to warm slowly until the entrained chlorine boiled away. Keeping the product cold (ice bath), the remaining trap contents were transferred to a 5 ml polypropylene tube and washed, first with 10% aqueous sodium sulfite (until a colorless mixture resulted), and then with 5% aqueous sodium carbonate (1×1 ml) and distilled water (2×1 ml). To maximize recovery, centrifugation was used to improve layer separation after each wash. The remaining water was removed by freezing the product mixture and decanting the liquid portion. The final product was a colorless, mobile liquid (density = 1.45 g ml^{-1}; b.p. 42 °C) obtained in 96% purity. Analysis identified the product as 1,2-bis(trifluoromethoxy)-1,1,3,3,3-pentafluoropropane (**2**, Scheme 1), which was obtained in 59% yield. GC–MS yielded the following fragments: m/z 217 ($M^+ - OCF_3$); 167 ($CF_3CHOCF_3^+$); 151 ($CF_3CHFCF_2^+$); 135 ($CF_3OCF_2^+$); 69 (CF_3^+, base peak). The abundance of the m/z 69 peak was pronounced, in accord with a product containing three CF_3 moieties. Proton, ^{19}F and ^{13}C NMR data are presented in Table 2. The remaining impurity was identified as a monochlorinated **2** by GC–MS; a similar fragmentation pattern to that of **2** was observed, with the addition of peaks at m/z 85/87 in a 1:0.29 ratio ($CClF_2^+$).

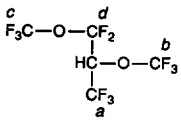
Table 2
NMR data for 1,2-bis(trifluoromethoxy)-1,1,3,3,3-pentafluoropropane (**2**)

^1H NMR data



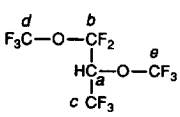
	Chemical shift (ppm)	Coupling constant (Hz)
	4.70 (sextet)	$^3J_{HF} = 5.40$

^{19}F NMR data



Fluorine	Chemical shift (ppm)	Coupling constant (Hz)
a	−55.8 (m, 3F)	
b and c	−61.0 (s, 3F)	
	−73.7 (s, 3F)	
d	−78.9 to −80.4 (AB pattern, 2F)	$^2J_{FF} = 148$

^{13}C NMR data



Carbon	Chemical shift (ppm)	Coupling constant (Hz)
a	72.2 (sextet)	$^3J_{CF} = 33.6$
b	117.2 (t)	$J_{CF} = 282.0$
c, d	119.2 (q)	$J_{CF} = 268.4$
and e	119.7 (q)	$J_{CF} = 282.1$
	120.9 (q)	$J_{CF} = 262.3$

2.5. *In vivo studies*

The use of animals in this study was approved by the University of Iowa Animal Care Committee. The CNS properties of the fluorinated compound were examined using a procedure slightly modified from that reported previously [11]. Briefly, a femoral venous catheter was surgically inserted into four male Sprague–Dawley rats (180–200 g). The catheter end was outfitted with a three-way connector to which was attached two syringes, one containing sterile, heparinized saline and the other containing test compound **2**. Due to the volatility of the test compound, the syringe used for its administration was cooled on ice prior to loading and until just before infusion. The catheter was cleared with 50 μl saline, test compound (15 or 25 μl, neat) was injected and the line was cleared with 100 μl additional saline.

To test **2** as a vapor, two rats were placed in a 2-l vacuum desiccator. The animals rested on a vented porcelain floor, below which was spread 125 g of soda lime CO_2 absorbent. The chamber was flushed with 100% oxygen using the vacuum port, which was then sealed with a septum. A volume of **2** sufficient to yield a concentration of 0.5% (v/v) was introduced into the chamber as a vapor through the septum. This was accomplished by loading a 5 ml syringe with the necessary amount of compound and then repeatedly forcing the headspace of the syringe into the desiccator until no liquid remained. The response of the animals was noted over a 15-min period, after which the atmosphere in the chamber was replenished with 100% oxygen followed by a second loading of 0.5% fluorinated compound B. The animals were continuously observed during another 15-min exposure period.

3. Results

Photochemical chlorination of compound B resulted in the rapid formation of numerous chlorinated compound B derivatives, evident from the detection of multiple fractions following gas chromatography. By allowing the reaction to proceed in the presence of excess chlorine, nearly pure **1** was obtained. Vacuum distillation readily removed a small amount of uncharacterized contaminant and provided the final product in excellent yield. The reaction resulted in the replacement of all five methoxy hydrogens; only the C-2 hydrogen remained.

Addition of BrF_3 to **1** resulted in a vigorous exothermic reaction and the evolution of substantial amounts of chlorine gas [6]. Maintenance of the reaction flask in an ice water bath and the addition of BrF_3 in small aliquots provided good control of the reaction, preventing the sudden formation of large amounts of Cl_2 and heat. The polyfluorinated product and reaction intermediates generated in this study were highly volatile, and necessitated the use of a Dry Ice/isopropanol cooled condenser to efficiently retain material in the reaction flask. Over the early course of the reaction, some material collected in the cold trap, however. This typically consisted of one major component (50%–75%, the higher values being obtained when using SbF_3), along with other putative polyfluorinated intermediates. By returning the impure material to the reaction flask, the purity of the subsequently collected major product was increased to 96%. The volatility of the product was advantageous, as the ability to employ a cold trap removed the need to isolate it from unreacted BrF_3.

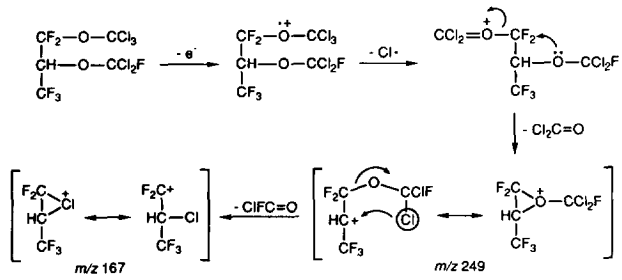
The efficacy of SbF_3 in the substitution of methoxy chlorine atoms by fluorine using BrF_3 was clearly demonstrated by the marked increase in the reaction rate. Although all five chlorines were successfully replaced by bromine trifluoride alone, the addition of SbF_3 provided equivalent yields and purity in 2–3 h less time. The increased vigor of the reaction (much more profuse release of Cl_2 upon initial additions of BrF_3) was also evident, and the rate at which the first several aliquots of BrF_3 were added was consequently reduced.

Whether given intravenously or as a vapor, **2** was highly toxic. Infusion of two animals with 25 μl iv resulted in an almost immediate cessation of respiration and death within 2 min. No convulsant activity was observed under these conditions. Administration of 15 μl to two animals yielded an identical result, although one animal exhibited a very brief seizure prior to death.

Exposure of rats to 0.5% (v/v) **2** vapor initially caused mild ptosis but no significant behavioral changes. The animals remained alert and continued normal movements for the first 15 min. Five minutes into the second exposure period an increasing degree of lethargy ensued. After 25-min total exposure, movement was only intermittent and piloerection and an apparent cyanosis were evident. One animal died before the conclusion of the 30-min exposure period; the other died within 10 min of removal from the chamber. Based on these findings and until its toxicity is further defined, BTPP must be considered highly toxic and handled with caution.

4. Discussion

The selective fluorination of carbon atoms is a reaction of significant industrial importance, notably in the manufacture of anesthetics [1]. Polyfluorinations represent a particular synthetic challenge. This study has demonstrated a straightforward means of perfluorinating the methoxy and fluoromethoxy groups of the diether compound B, using bromine trifluoride and the intermediacy of a chlorinated derivative



Scheme 2. Possible fragmentation pathway leading to the m/z 249 and 167 fragments in the mass spectrum of the chlorinated compound B derivative **2**. Not all canonical forms of the ions are shown.

(Scheme 1). The fluorination rate may be enhanced by SbF_3. The resulting fluorinated diether, **2**, exhibited greatly increased volatility versus compound B. The toxicity of **2** precluded evaluation of its metabolic stability in vivo, however.

Evidence for the pentachlorination and subsequent pentafluorination of compound B was provided by GC–MS and NMR methods. The ^1H NMR spectra of both compounds clearly show the presence of only one proton signal, which appears as a sextet in both cases due to the similar coupling constants to both sets of adjacent fluorines. A possible fragmentation pathway for the chlorinated compound **1**, leading to the m/z 249/251 and 167/169 (base peak) fragment pairs, is shown in Scheme 2. This interpretation is consistent with the observed M+2 and M+4 intensity pattern [20], which indicate that the m/z 249 fragment contains two chlorines and the m/z 167 fragment contains one. The formation of an m/z 249 fragment also points to the preferential loss of a chlorine radical from the trichloromethoxy group, as initial loss of chlorine (or fluorine) from the dichlorofluoromethoxy group would be expected to yield an oxonium ion with m/z 265. Operation of an analogous pathway would account for the m/z 217 and 151 fragments from **2**.

Numerous aliphatic ethers have been fluorinated using BrF_3. In cases where the α carbon is a CH_3 or CH_2 moiety, reaction with BrF_3 usually results exclusively in monofluorination at this position. For example, $CH_3OCF_2CH(CF_3)OCH_2F$ gives only $CH_2FOCF_2CH(CF_3)OCH_2F$ [11] and $(CF_3)_2CHCF_2OCH_2CH_3$ gives $(CF_3)_2CHCF_2OCHFCH_3$ [7]. While it is known that BrF_3 will also replace chlorine with fluorine [9,21], the potential of α-chlorinated ethers to undergo BrF_3 fluorination has not been thoroughly explored. The α-chloroethers $(CF_3)_2CHOCH_2Cl$ and $CF_3CHClOCHF_2$ yield $(CF_3)_2CHOCH_2F$ (sevoflurane) [22] and $CF_3CHFOCHF_2$ (desflurane) [8,23], respectively. The α,α-dichloroether $CF_3CHFOCHCl_2$ may also be reacted with BrF_3 to access desflurane [24]. The findings of this study extend the chemistry of BrF_3, demonstrating its ability to directly convert trichloromethoxy and dichlorofluoromethoxy groups to a trifluoromethoxy moiety. This method supplements the sequential reactions of an alcohol with carbonyl

fluoride and sulfur tetrafluoride [25] as a synthetic approach to trifluoromethyl ethers.

Although BrF_3 is often reactive enough to be used without a catalyst, the Lewis acids $SnCl_4$, $SbCl_5$ and SbF_3 have been used to improve reaction rates and selectivity [6,9]. Antimony trifluoride served an apparent catalytic function in the reaction of **2** with BrF_3. The mechanism by which this catalysis operates is unclear, although SbF_3 is thought to react with the chlorine source in situ to generate SbF_3Cl_2 which serves as the ultimate catalyst [9].

The toxicity of **2** demonstrates how the CNS effects of similar polyfluorinated compounds can be dramatically different [12,13,15]. While BFPP containing an identical diether backbone is a hypnotic/sedative [11], **2** is lethal. Such a range of pharmacological activity has also been observed among the many monoethers examined for CNS activity [13]. The compounds $CH_3OCF_2CHCl_2$ (methoxyflurane) and CH_3OCF_2CHBrF (roflurane) [26], for example, are both excellent anesthetics; $CH_2ClOCF_2CHF_2$ and $CF_2ClOCF_2CFCl_2$, however, are both toxic [13,27]. While both $CF_3CH_2OCF_2CHF_2$ and $CF_3CH_2OCH_2CF_3$ (indoklon) are potent convulsants [13,28,29], $CF_3CF_2OCF_2CF_3$ is devoid of effects at concentrations up to 75% (v/v) [15] and $CH_3CH_2OCF_2CHF_2$ is an anesthetic [30]. One of the few ethers containing a trifluoromethoxy group tested in vivo, i.e. $CF_3OCH_2CF_2CH_2F$, causes convulsions and death in mice when inhaled at a concentration of 0.5% (v/v) [25,31]. The brief seizure observed in one animal administered **2** suggests that it also possesses some degree of convulsant activity.

In summary, this report demonstrates the potential of polychlorinated methoxy groups in methyl ethers to serve as a vehicle for the synthesis of polyfluorinated analogs using bromine trifluoride. Antimony trifluoride may improve reaction rates. The use of analogous brominated and iodinated intermediates, as well as other possible catalysts, remains untested. The novel fluorinated diether **2** generated in this study exhibits completely different CNS effects than both its precursor, compound B, and the compound B derivative BFPP.

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References

[1] D.F. Halpern, in R. Filler, Y. Kobayashi and L.M. Yagupolskii (eds.), *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, 1993.
[2] D.F. Halpern and M.L. Robin (to BOC, Inc.), US Pat. 4 996 371, 1991.
[3] T.E. Stevens, *J. Org. Chem., 26* (1961) 1627.
[4] R.A. Davis and E.R. Larson, *J. Org. Chem., 32* (1967) 3478.
[5] R.A. Davis and E.R. Larson (to Dow Chemical Co.), Br. Pat. 1 059 234, 1967.
[6] A.V. Kartashov, N.N. Chuvatkin and L.S. Boguslavskaya, *Zh. Org. Khim., 24* (1988) 2522.
[7] V.S. Yuminov, L.N. Pushkina and S.V. Sokolov, *Zh. Obshch. Khim., 37* (1967) 375.
[8] M.L. Robin and D.F. Halpern (to BOC, Inc.), US Pat. 5 015 781, 1991.
[9] C. Huang and G.G. Vernice (to BOC, Inc.), US Pat. 4 874 902, 1989.
[10] M.T. Baker, C.-K. Chiang and J.H. Tinker, *J. Labelled Compd. Radiopharm., 33* (1993) 801.
[11] J.A. Ruzicka, J.B. Hrdy and M.T. Baker, *J. Fluorine Chem.*, in press.
[12] B.H. Robbins, *J. Pharmacol. Exp. Ther., 86* (1946) 197.
[13] E.R. Larsen, in P. Tarrant (ed.), *Fluorine Chem. Rev.*, Marcel Dekker, New York, 3 (1969).
[14] E.I. Eger, J. Lui, D.D. Koblin, M.J. Laster, S. Taheri, M.J. Halsey, P. Ionescu, B.S. Chortkoff and T. Hudlicky, *Anesth. Analg., 79* (1994) 245.
[15] G. Lu, S.L. Johnson, M.S. Ling and J.C. Krantz, *Anesthesiology, 14* (1953) 466.
[16] T.H.S. Burns, J.M. Hall, A. Bracken, G. Goldstone and D.S. Newland, *Anæsthesia, 16* (1961) 3.
[17] M. Morio, K. Fujii, N. Satoh, M. Imai, U. Kawakami, T. Mizuno, Y. Kawai, Y. Ogasawara, T. Tamura, A. Negishi, Y. Kumagai and T. Kawai, *Anesthesiology, 77* (1992) 1155.
[18] E.J. Frink, T.P. Malan, S.E. Morgan, E.A. Brown, M. Malcomson and B.R. Brown, *Anesthesiology, 77* (1992) 1064.
[19] C. Huang, V.S. Venturella, A.L. Cholli, F.M. Venutolo, A.T. Silbermann and G.G. Vernice, *J. Fluorine Chem., 45* (1989) 239.
[20] R.M. Silverstein, G.C. Bassler and T.C. Morril, *Spectrometric Identification of Organic Compounds*, 5th edn., John Wiley & Sons, New York, 1991, Chap. 2.
[21] B.M. Regan (to Baxter Laboratories, Inc.), US Pat. 3 773 840, 1973.
[22] B.M. Regan and J.C. Longstreet (to Baxter Laboratories, Inc.), US Pat. 3 683 092, 1972.
[23] R.C. Terrell (to BOC, Inc.), US Pat. 4 762 856, 1988.
[24] L.A. Rozov, C. Huang and G.G. Vernice (to Anaquest, Inc.), US Pat. 5 205 914, 1992.
[25] P.E. Aldrich and W.A. Sheppard, *J. Org. Chem., 29* (1963) 11.
[26] R.C. Terrell (to Air Reduction Co.) US Pat. 3 586 724, 1971.
[27] A. Van Poznak and J.F. Artusio, *Toxicol. Appl. Pharmacol., 2* (1960) 374.
[28] J.C. Krantz, A. Esquibel, E.B. Truitt, A.S.C. Ling and A.A. Kurland, *J. Am. Med. Assoc., 166* (1958) 1555.
[29] J.C. Krantz, A. Esquibel, E.B. Truitt, A.S.C. Ling and A.A. Kurland, *Toxicol. Appl. Pharmacol., 1* (1959) 362.
[30] T.H.S. Burns, J.M. Hall, A. Bracken, G. Gouldstone and D.S. Newland, *Anesthesia, 16* (1961) 3.
[31] B.M. Regan (to Baxter Laboratories), US Pat. 3 689 459, 1972.