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3,499,089

**METHOD OF INDUCING ANESTHESIA WITH
2-HALO-1,1,1,3,3-PENTAFLUOROPROPANES**Bernard M. Regan, Chicago, Ill., assignor to Baxter
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2 Claims

ABSTRACT OF THE DISCLOSURE

2-chloro-1,1,1,3,3-pentafluoropropane and 2-bromo-1,1, 15
1,3,3-pentafluoropropane, useful as nonflammable inhala-
tion anesthetics, and the intermediate 1,1,1,3,3-pentafluoro-
propan-2-ol and p-toluenesulfonate ester of said alcohol
used in preparing the inhalation anesthetics.

This invention relates to novel halopentafluoropropanes.
More particularly, this invention relates to certain mono-
halopentafluoropropanes having a chlorine or bromine
atom substituted on the number two carbon atom, name-
ly, 2-chloro-1,1,1,3,3-pentafluoropropane and 2-bromo-
1,1,1,3,3-pentafluoropropane.

It is known that certain halogenated alkanes are useful
inhalation anesthetics. Chloroform and halothane are
well-known examples of such compounds which are deriva-
tives of the lower alkanes, methane and ethane, respec-
tively. More recently, it has also been disclosed that cer-
tain halogenated propanes are useful inhalation anes-
thetics. Thus, Dishart, U.S. Patent 3,034,959, discloses the
inhalation anesthetic use of 2-bromo-1,1,2,2-tetrafluoro-
propane and Belgian Patents 663,478 and 668,605 dis-
close the inhalation anesthetic use of 3-bromo-3-chloro-
1,1,1,2,2-pentafluoropropane.

Position isomers of the monohalopentafluoropropanes
of the present invention also are known. Thus, 3-bromo-
and 3-chloro-1,1,1,2,2-pentafluoropropanes are disclosed
by McBee et al., 77, J. Am. Chem. Soc'y. 3149 (1955);
3-bromo-1,1,1,3,3-pentafluoropropane is disclosed by
Murray, British Patent 908, 110; 3-chloro-1,1,1,3,3-penta-
fluoropropane is disclosed by Henne et al., 68, J. Am.
Chem. Soc'y. 496 (1946) and Arnold, U.S. Patent 2,558,-
703; 3-bromo- and 3-chloro-1,1,2,2,3-pentafluoropropanes
and 1-bromo- and 1-chloro-1,1,2,2,3-pentafluoropropanes
are disclosed in a dissertation by Beck, "Reactivities of
Aliphatic Fluorides," The Ohio State University (1959);
and 2-bromo-1,1,1,2,3-pentafluoropropane is disclosed by
Rausch et al.; 28, J. Org. Chem. 494 (1963).

Three of the above position isomers of the monohalo-
pentafluoropropanes of the present invention have been
further disclosed as having inhalation anesthetic proper-
ties. Thus, Raventos, British Patent 913,143, discloses the
inhalation anesthetic properties of 3-bromo-1,1,1,3,3-
pentafluoropropane and Burns et al., 17, Anaesthesia 337-
43 (1962), disclose the inhalation anesthetic properties
of the 3-bromo- and 3-chloro-1,1,1,2,2-pentafluoropro-
panes.

It has now been found that the novel monohalopenta-
fluoropropanes having a chlorine or a bromine atom sub-
stituted on the number two carbon atom, as defined here-
in, are useful inhalation anesthetics which have inhalation
margins of safety in mice which are substantially higher

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than the margins of safety of the inhalation anesthetics
in current use, namely, ether, chloroform, and halothane.
Moreover, these margins of safety of the novel monohalo-
pentafluoropropanes of this invention are also substan-
tially higher than the margins of safety of the above-
mentioned position isomers disclosed by Raventos and
Burns et al. As such, the compounds of this invention
hold good promise as effective and useful agents for in-
ducing anesthesia in man.

The novel inhalation anesthetic compounds of this in-
vention also have been found to be nonflammable in air
at ambient temperatures and nonexplosive in oxygen. The
flammability margins of safety of these compounds in
oxygen are substantially higher than the margins of safety
of the above-mentioned position isomers of these com-
pounds which are disclosed by Burns et al. as having in-
halation anesthetic properties.

The anesthetic compounds of the present invention can
be administered by apparatus or machines designed for
the vaporization of liquid anesthetics and admixtures
thereof with oxygen, air or other gaseous mixtures con-
taining oxygen in amounts capable of supporting res-
piration.

The novel 2-chloro-1,1,1,3,3-pentafluoropropane boils
at 39° C. and the novel 2-bromo-1,1,1,3,3-pentafluoro-
propane boils at 57.5° C. Each of these compounds can
be conveniently stored in containers normally used for
conventional inhalation anesthetics of comparable boiling
points, e.g., ether, chloroform and halothane.

For use in anesthesia, the compounds of the present
invention should be free from toxic impurities which may
be present according to the particular process used for
their manufacture. These compounds can, however, be
used in admixture with pharmaceutically acceptable sub-
stances such as stabilizers, e.g., thymol, or one or more
of the known inhalation anesthetics, e.g., nitrous oxide,
ether, halothane, chloroform, cyclopropane, methoxyflu-
orane and the like.

The novel monohalopentafluoropropanes defined herein
can be conveniently prepared from a suitable alkali metal
halide and the p-toluenesulfonate ester of 1,1,1,3,3-penta-
fluoropropan-2-ol by reaction at about 210° C. to about
230° C. in a suitable diluent followed by separation of the
desired products from the reaction mixture.

Potassium bromide is the preferred alkali metal halide
used for the preparation of 2-bromo-1,1,1,3,3-pentafluoro-
propane and lithium chloride is the preferred alkali
metal halide used for the preparation of 2-chloro-1,1,1,
3,3-pentafluoropropane. Other alkali metal halides can be
substituted for the above potassium bromide and lithium
chloride provided that they are sufficiently soluble in the
diluent to provide suitable reaction. Generally, from about
one to about two moles of the alkali metal halide are
used per mole of p-toluenesulfonate ester in the above
reaction.

Examples of suitable diluents for use in the above re-
action are: sulfones such as diethyl sulfone, dimethyl
sulfone and tetramethylene sulfone.

Although a reaction temperature of from about 210°
C. to about 230° C. is described above, it will be under-
stood that there can be some variation in this tempera-
ture, depending upon the boiling point of the diluent and
other conditions of the reaction.

Upon completion of the above reaction, the desired
products can be separated from the other reaction prod-
ucts by fractional distillation with or without prior wash-

ings with water. An oxidant, for example, hydrogen peroxide or potassium permanganate, can be employed prior to distillation of the desired products to remove undesirable impurities, such as sulfides derived from the sulfone solvents used in the preparation of the mono-halopentafluoropropanes of this invention.

The intermediate p-toluenesulfonate ester of 1,1,1,3,3-pentafluoropropan-2-ol which is used to prepare the novel inhalation anesthetics defined herein also is a novel compound. It can be conveniently prepared by reacting a mixture of 1,1,1,3,3-pentafluoropropan-2-ol and an equimolar equivalent of p-toluenesulfonyl chloride with a slight molar excess of sodium hydroxide or similar such alkali in water, preferably at about 20° C. to about 40° C., and then separating the 1,1,1,3,3-pentafluoro-2-propyl p-toluenesulfonate from the other reaction products.

The intermediate 1,1,1,3,3-pentafluoropropan-2-ol which is used to prepare the novel inhalation anesthetics defined herein also is a novel compound. It can be conveniently prepared by reduction of chloropentafluoroacetone with about five molar equivalents of hydrogen and a catalyst of palladium on carbon, preferably in the vapor phase at about 180° C., and then separating the desired 1,1,1,3,3-pentafluoropropan-2-ol from the other reaction products by fractional distillation.

The novel 1,1,1,3,3-pentafluoropropan-2-ol defined herein also is useful as a solvent, particularly for compounds that contain receptive sites for the strong hydrogen-bonding donor properties of this alcohol. Among these compounds are polymers such as polyformaldehyde, nylon and other polyamides, polyacrylonitrile, polyvinyl alcohol, and polyesters. The novel alcohol also is a solvent for natural products containing amide, amino, ester, alcohol or ketone groups.

Although the above methods of preparation and reaction conditions are specifically described, it will be understood that the novel compounds of this invention are not limited to these specific reaction conditions or to these specific methods of preparation.

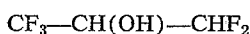
The following examples will further illustrate the present invention, although the invention is not limited to these specific examples. All percentages and parts herein are on a weight basis unless otherwise specified.

EXAMPLE I

1,1,1,3,3-pentafluoropropan-2-ol (I)

Hydrogen at the rate of one liter per minute and the vapor of chloropentafluoroacetone at the rate of 1.5 grams per minute were mixed and passed through a Pyrex tube (45 cm. x 1.9 cm. I.D.) containing 2% palladium on carbon granules (4-12 mesh) and heated to 180° C. The reaction products were condensed in a trap cooled by Dry Ice.

In a typical run 480 grams (2.63 moles) of chloropentafluoroacetone was vaporized with hydrogen during 5.5 hours, and the mixture passed over 85 grams of palladium-carbon catalyst. Fractional distillation of the 358 grams of reaction products gave 258 grams (1.72 moles, 65% of theory) of crude alcohol (I), B.P. 81° C. Its infrared spectrum is consistent with the



structure.

Analysis.—Calc'd for $\text{C}_3\text{H}_3\text{F}_5\text{O}$: C, 24.01%; H, 2.04%. Found: C, 23.99%; H, 2.18%.

EXAMPLE II

1,1,1,3,3-pentafluoro-2-propyl p-toluenesulfonate (II)

A mixture of crude 1,1,1,3,3-pentafluoropropan-2-ol (I) (750 grams, 5.00 moles), p-toluenesulfonylchloride (954 grams, 5.00 moles) and 1200 ml. of water was stirred as 5 N sodium hydroxide solution (1050 ml., 5.25 moles) was added during about 3 hours, and the temperature was maintained between 25°-40° C. Stirring was continued for about 16 hours. The crude ester (II) was separated, stirred, evacuated to between 25-40 mm.

Hg and heated to 125° C. until volatile impurities ceased to distill. About 1445 grams (4.75 moles, 95% of theory) of crude tosyl ester (II) was obtained. Crystallization from petroleum ether gave purified tosyl ester (II), M.P. 26° C.

Analysis.—Calc'd for $\text{C}_{10}\text{H}_9\text{F}_5\text{O}_3\text{S}$: C, 39.48%; H, 2.98%; F, 31.22%; S, 10.54%. Found: C, 39.50%; H, 3.21%; F, 32.67%; S, 11.51%.

EXAMPLE III

2-bromo-1,1,1,3,3-pentafluoropropane (III)

To a stirred mixture of potassium bromide (450 grams, 3.78 moles) in 1250 grams of dimethyl sulfone heated to 225° C., crude 1,1,1,3,3-pentafluoro-2-propyl p-toluenesulfonate (II) (770 grams, 2.53 moles) was added. As III formed, it distilled through a Vigreux column and descended through a cold-water spiral condenser. The product was collected in an ice-cooled receiver and washed with water to yield 310 grams (1.46 moles, 58% of theory) of crude III having an unpleasant sulfide-like odor. It was treated with 50 ml. of acidified 10% potassium permanganate solution with stirring at room temperature overnight. The bromide III was separated, washed with water, dried by azeotropic distillation and fractionally distilled to give about 242 grams (1.14 moles, 45% of theory) of III, b_{740} 56.6-57.0° C., d_4^{20} 1.8637 and n_D^{20} 1.3332. It was found to be 99.6% pure by gas-liquid partition chromatography. Its 60 MC nuclear magnetic resonance and infrared spectra confirm the



structure.

EXAMPLE IV

2-chloro-1,1,1,3,3-pentafluoropropane (IV)

To a stirred mixture of potassium chloride (200 grams, 2.69 moles) and 865 grams of dimethylsulfone heated to 225° C., crude 1,1,1,3,3-pentafluoro-2-propyl-p-toluenesulfonate (530 grams, 1.73 moles) was added. Very little product distilled during 2 hours, so the reaction mixture was cooled and anhydrous lithium chloride (42.4 grams, 1.00 mole) was added. Upon heating the reaction mixture to 225° C., product began distilling at a reasonable rate. Altogether 157 grams (0.93 mole, 54% of theory) of crude IV was collected. It was washed with water and stirred with 50 ml. of acidified 10% potassium permanganate solution overnight at room temperature. The chloride IV was separated, washed with water, dried by azeotropic distillation and fractionally distilled to give 118.5 grams (0.70 mole, 41% of theory) of IV, b_{750} 38.2-38.6° C. A fraction of this assaying 99.7% by gas-liquid partition chromatography has d_4^{20} 1.5059 and n_D^{20} 1.3010. Its nuclear magnetic resonance and infrared spectra confirm the $\text{CF}_3\text{—CHCl—CHF}_2$ structure.

EXAMPLE V

Inhalation of the vapor of 2-bromo-1,1,1,3,3-pentafluoropropane or 2-chloro-1,1,1,3,3-pentafluoropropane admixed with air according to the procedure described by Robbins, 86 J. Pharmacol. Exper. Therap. 197-204 (1946), produced anesthesia in white mice. The minimum concentration by volume percent needed to produce full anesthesia in 50% of the mice in five minutes, AC_{50} , and the minimum concentration by volume percent needed to kill 50% of the mice in five minutes, LC_{50} , are given in Table I, below. The inhalation margin of safety as calculated for mice by the $\text{LC}_{50}/\text{AC}_{50}$ ratio is also given for the above compounds. For purposes of comparison, similar data which were obtained under the same conditions as for the above compounds are given for three inhalation anesthetics in current use, viz, ether, chloroform, and halothane, and for the 3-bromo-pentafluoropropanes which are position isomers of the inhalation anesthetic compounds of this invention and disclosed by Raventos and Burns et al. as having inhalation anesthetic properties. The number of mice used with the

different agents varied from 25 to 92 for determining each of the AC₅₀ and LC₅₀ doses.

TABLE 1.—INHALATION ANESTHESIA IN MICE

Compound	AC ₅₀	LC ₅₀	LC ₅₀ /AC ₅₀
CF ₃ —CHBr—CHF ₂	0.52	3.10	6.0
CF ₃ —CHCl—CHF ₂	1.00	6.57	6.6
Ether.....	3.69	12.0	3.2
Chloroform.....	0.94	2.56	2.7
Halothane.....	0.78	2.62	3.4
CF ₃ CH ₂ —CF ₂ Br.....	1.62	5.84	3.6
CF ₃ —CF ₂ —CH ₂ Br.....	1.71	5.58	3.3

The results set forth in the above table show a substantial and significant improvement in the inhalation margin of safety of the inhalation anesthetic compounds of this invention compared to the three inhalation anesthetics in current use and to the isomeric 3-bromo-pentafluoropropanes.

EXAMPLE VI

Four dogs were anesthetized with 2-bromo-1,1,1,3,3-pentafluoropropane at concentrations ranging from 0.5 to 1.5 volume percent in admixture with oxygen. For purposes of comparison, five dogs were anesthetized under the same conditions with halothane at concentrations ranging from 1 to 2 volume percent in admixture with oxygen. The higher concentrations of the anesthetics were the amounts required to induce full anesthesia and the lower concentrations were the amounts required to maintain surgical anesthesia (stage III, plane 2) in the animals.

The anesthetic mixture was administered via an endotracheal catheter with inflation cuffs in a non-rebreathing system subsequent to initial anesthesia with sodium methohexital and pretreatment with atropine sulfate and heparin.

Heart rate and myocardial responses were determined from EKG records. Spontaneous respiratory rate and respiratory minute volume were monitored by means of a pressure change transducer and a wet-test meter, respectively. The arterial blood pressure was monitored, and blood samples were withdrawn for determinations of blood gases and pH.

Anesthesia with 2-bromo-1,1,1,3,3-pentafluoropropane was substantially equivalent to anesthesia with halothane. Both compounds produced a fall in diastolic blood pressure below 70 mm. Hg in three dogs and a decrease in heart rate. Normal respiratory minute volume and normal *p*CO₂ values were observed for both compounds in four out of four dogs. The EKG records were normal for both compounds, with the exception that T-wave inversion occurred in three out of four dogs with 2-bromo-1,1,1,3,3-pentafluoropropane and in four out of five dogs with halothane.

After thirty and sixty minutes of surgical anesthesia, the 2-bromo-1,1,1,3,3-pentafluoropropane and halothane were compared in their effects on the heart beat following intravenous administration of epinephrine in sequential 0.3 log dose increments over a range of 0.25 µg./kg. to 32 µg./kg. at five minute intervals. Subsequent to the administration of epinephrine, 2-bromo-1,1,1,3,3-pentafluoropropane was shown to possess anesthetic properties superior to halothane. Arrhythmias of long duration occurred frequently with halothane even at small doses of epinephrine. A dose of 4 µg. of epinephrine per kilogram of body weight consistently fibrillated dogs under halothane anesthesia. In contrast, a dose of 8 µg. of epinephrine per kilogram of body weight were required to induce brief arrhythmias in two of four dogs and a dose of 16 µg./kg. caused fibrillation in only one of four dogs under anesthesia with 2-bromo-1,1,1,3,3-pentafluoropropane.

The above property of 2-bromo-1,1,1,3,3-pentafluoropropane, whereby said compound has substantially less tendency than halothane to sensitize the heart to the ac-

tion of epinephrine, indicates the usefulness of this novel anesthetic agent in cases where the surgeon desires to administer epinephrine.

EXAMPLE VII

The flammability of gaseous mixtures of the novel inhalation anesthetics of the present invention and air or oxygen was determined at room temperature and atmospheric pressure by visualization of the downward propagation of a flame in a glass bottle having a cylindrical portion 2.3 inches I.D. x 3.5 inches in height. The bottle was flushed with pure oxygen or air, a known quantity of liquid anesthetic added rapidly, and the bottle closed with a ground glass stopper. The bottle was then rotated and shaken until the liquid anesthetic was completely vaporized and uniformly mixed with oxygen or air. The stopper was then removed and immediately a burning stick inserted in the bottle 1.5 to 2.0 inches below the bottle mouth.

The concentration by volume percent of the gaseous anesthetic in oxygen or air was calculated by well-known computation means employing the known volume of the stoppered bottle (i.e., the volume of the contained oxygen or air), the known volume of the added liquid anesthetic, the known densities and molecular weights and application of the ideal gas law to compute the gaseous volume of the anesthetic sample.

The lower flammability limits in oxygen, LFI_{O2}, and in air, LFI_{air}, as determined by the above procedure are given in Table 2, below. These flammability limits are stated as a range of two concentrations by volume percent of the anesthetic in the gaseous mixture; downward flame propagation was observed at the higher concentration but not at the lower concentration. The median anesthetic concentrations for mice, AC₅₀, as determined in Example V, above, are also given in Table 2. The ratio, LFI_{O2}/AC₅₀, herein referred to as the flammability margin of safety, is also given in Table 2. For purposes of comparison, similar data for flammability in oxygen which were obtained under the same conditions as for the above compounds are given for the position isomers 3-bromo- and 3-chloro-1,1,1,2,2-pentafluoropropanes, which are disclosed by Burns et al., as having inhalation anesthetic properties.

TABLE 2.—FLAMMABILITY OF ANESTHETICS

Compound	LFI _{O2}	LFI _{air}	AC ₅₀	LFI _{O2} /AC ₅₀
CF ₃ —CHBr—CHF ₂	14.0-14.5	Nonflamm....	0.52	27
CF ₃ —CHCl—CHF ₂	13.0-13.7	Nonflamm....	1.00	13
CF ₃ —CF ₂ —CH ₂ Br.....	11.0-11.6	(1).....	1.71	6.5
CF ₃ —CF ₂ —CH ₂ Cl.....	10.4-11.0	(1).....	5.69	1.9

¹ Not tested.

The results set forth in the above table show that the novel monohalopentafluoropropanes of this invention have substantially greater flammability margins of safety than shown by the position isomers 3-chloro- and 3-bromo-1,1,1,2,2-pentafluoropropanes.

What is claimed is:

1. The method of inducing anesthesia in animals which comprises administering by inhalation to said animals an effective amount of an organic monohalopentafluoropropane having the formula:



in which X is selected from the group consisting of chlorine and bromine.

2. The method of inducing anesthesia in animals which comprises administering by inhalation to said animals a gaseous, nonflammable mixture of an organic monohalopentafluoropropane having the formula:



in which X is selected from the group consisting of chlorine and bromine and oxygen in suitable proportions for the production of anesthesia and maintenance of respiration.

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