

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 November 2009 (05.11.2009)

PCT

(10) International Publication Number
WO 2009/133575 A1

(51) International Patent Classification:
C07C 41/16 (2006.01) C07C 43/12 (2006.01)

(21) International Application Number:
PCT/IT2008/000293

(22) International Filing Date:
28 April 2008 (28.04.2008)

(25) Filing Language: Italian

(26) Publication Language: English

(71) Applicant (for all designated States except US):
AL.CHIL.MI.A. S.r.l. [IT/IT]; Viale Austria 14, I-35020
PONTE S. NICOLO' (PADOVA) (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CONTE, Lino
[IT/IT]; Via P. Leopoldo 15, I-35028 PIOVE DI SACCO
(PADOVA) (IT). ZAGGIA, Alessandro [IT/IT]; Via
Sette Martiri 132/D, I-35100 PADOVA (IT). BECCA-
RO, Mauro [IT/IT]; Via Trieste 22, I-35010
CADONEGHE (PADOVA) (IT). BETTINI, Enrico
[IT/IT]; Via Zuina, I-30032 FIESSO D'ARTICO
(VENEZIA) (IT). SIGNORI, Paolo [IT/IT]; Via
Belvedere 10, I-37131 VERONA (IT).

(74) Agent: MARGUTTI, Roberto; C/o Bugnion S.p.A.,
Viale Lancetti 17, I-20158 Milano (IT).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ,
EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG,
SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: FLUOROALKYLOXY ALKANES, PROCESS FOR PRODUCTION AND USES THEREOF

(57) Abstract: The present invention relates to fluoroalkyloxy alkanes having formula (I) : $R_F-R_1-O-R_2$ wherein: R_F is a linear or branched perfluoroalkyl group, having from 1 to 12, preferably from 2 to 8, carbon atoms; R_1 is a linear or branched, non-fluorinated alkylene group, having from 1 to 6, preferably from 2 to 4, carbon atoms, - R_2 is a linear or branched, non-fluorinated alkyl group, having from 1 to 12, preferably from 2 to 8, carbon atoms, possibly containing at least one ether bond -O- along the chain. The present invention further relates to a process for preparation and use thereof, possibly in mixture with at least one silicone oil, as medicaments in ophthalmology, in particular as tamponade liquids in an operation for the treatment of retinal detachment.



WO 2009/133575 A1

-1-

FLUOROALKYLOXY ALKANES, PROCESS FOR PRODUCTION AND USES THEREOF

The present invention relates to fluoroalkyloxy alkanes, to their synthesis process and to the use thereof for medical applications, in particular as liquids in ophthalmic treatments.

It is known about the use of liquid perfluorocarbons in ophthalmology, e.g. as tamponade liquids in operations for the treatment of retinal detachment or as vitreous body substitutes (see for instance patent application EP 0 089 232 A2).

Thanks to their high density (generally above 1.6 g/cm³) and to their extremely low surface tension (below 25 mN/m), liquid perfluorocarbons allow a complete unfolding and a correct re-positioning of the retina so as to favor the re-adhesion thereof. Perfluorocarbons are temporarily chemically inert and physiologically biocompatible products, if completely fluorinated. As a matter of fact, the presence, if any, of -CHF-CF₂- groups can give rise to dehydrofluorination with HF formation, resulting in the subsequent reduction of biocompatibility. Moreover, after their action as tamponade liquids during surgery is ended, perfluorocarbons cannot be kept in contact with the retina for long, since the high density can give rise, in

-2-

time, to phenomena of thinning of the lower retina. Therefore, the use of perfluorocarbons is recommended only intra-surgically. If left in the eye also after surgery, these should anyhow be removed and replaced
5 with a permanent tamponade liquid, such as a silicone oil.

It is known about the use of silicone oils (in particular polydimethylsiloxane) as tamponade liquids during ophthalmic surgery. These products, however,
10 have some limitations related in particular to the fact that silicone oils have too low a density, usually of about 0.97 g/cm^3 and thus lower than water density, and cannot ensure a sufficient pressure in the retina, especially the lower retina, since they
15 tend to come to the surface of the aqueous medium constituting the vitreous body.

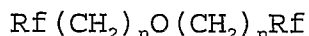
Recently, other fluorinated compounds have been proposed as liquids that can be used in ophthalmic applications.

20 For instance, patent US 6,262,126 B1 describes partially fluorinated alkanes with formula $R_F R_H$ or $R_F R_H R_F$, wherein R_F is a linear or branched perfluoroalkyl group and R_H is a linear or branched, saturated alkyl group. The number of carbon atoms in the per-
25 fluorinated moiety can vary from 1 to 20, whereas for

-3-

the alkyl moiety the number of carbon atoms is usually from 3 to 20. These products are obtained by reaction of perfluoroalkyl iodides with alkenes or α,ω -dienes, with HI elimination, and subsequent hydrogenation in the presence of a platinum catalyst or by reaction with tributyltin hydride. These products have a density generally of from 1.1 to 1.7 g/cm³, thus lower than the density of perfluoroalkanes. Since they have a certain solubility in non-fluorinated compounds, they can be used as tamponade liquids in mixture with silicone oils, with the goal of obtaining a density slightly higher than water.

International patent application WO 2005/117850 describes partially fluorinated ethers and the use thereof as tamponade agents in mixture with a liquid silicone or a liquid perfluorocarbon. These partially fluorinated ethers have a specific gravity of from 1.1 to 1.5 and the following formula:



wherein Rf is a fluorinated, monovalent, saturated organic C1-C4 group and n is 3 or 4. Decafluoro-di-n-pentyl ether (DFPE) is particularly preferred. Preferably, the mixture comprises from 10 to 20% of DFPE and from 80 to 90% of silicone oil.

The Applicant has faced the problem of finding

-4-

liquids with high biocompatibility, high purity degree and suitable density values so that they can be used as liquids in ophthalmic treatments, in particular as tamponade liquids during surgical operations on the retina, which are able to exert a sufficient pressure during said operation so as to enable a correct re-positioning and a sufficient adhesion of the retina to the adjacent eye components, and which can be retained at the same time inside the eye structure for an undetermined lapse of time without damaging the retina itself.

The Applicant has found that this aim and others of the invention can be achieved by way of fluoroalkyloxy alkanes as defined hereinbelow, which both meet the above requirements and have a high solubility in unfluorinated liquids, in particular silicone oils, so as to enable the preparation of mixtures in a wide range of concentrations, which are stable at working temperatures, as better described in the following, without showing phase separation.

According to a first aspect, the present invention therefore relates to fluoroalkyloxy alkanes having formula (I):



wherein:

-5-

R_F is a linear or branched perfluoroalkyl group, having from 1 to 12, preferably from 2 to 8, carbon atoms;

R_1 is a linear or branched, non-fluorinated alkylene group, having from 1 to 6, preferably from 2 to 4, carbon atoms;

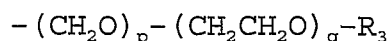
R_2 is a linear or branched, unfluorinated alkyl group, having from 1 to 12, preferably from 2 to 8, carbon atoms, possibly containing at least one ether bond -O- along the chain.

Preferably, R_F is a linear perfluoroalkyl group having formula $CF_3(CF_2)_n-$, wherein n is an integer from 1 to 12, more preferably from 2 to 8.

Preferably, R_1 is a linear alkylene group having formula $-(CH_2)_r-$, wherein r is an integer from 1 to 6, preferably from 2 to 4.

Preferably, R_2 is a linear, non-fluorinated alkyl group having formula $CH_3(CH_2)_m-$, wherein m is an integer from 1 to 12, more preferably from 2 to 8.

Optionally, R_2 may contain at least one ether bond along the chain; for instance, R_2 can have the following formula:



wherein: R_3 is $-CH_3$ or $-C_2H_5$; p is zero or an integer from 1 to 4; q is an integer from 1 to 4; the $-CH_2O-$

-6-

and $-\text{CH}_2\text{CH}_2\text{O}-$ groups being statistically distributed along the chain.

Particularly preferred fluoroalkyloxy alkanes having formula (I) are: $\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$,
5 $\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$, $\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$, and
 $\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$.

Preferably, fluoroalkyloxy alkanes having formula (I) have a density which may vary from 1.2 to 1.5 g/cm^3 , measured at 20°C .

10 According a second aspect, the present invention relates to a process for preparing a fluoroalkyloxy alkane having formula (I), which comprises reacting a fluorinated alcohol having formula (II):



15 wherein R_F and R_1 are as defined above, with an alkyl halide having formula (III):



wherein R_2 is as defined above and X is a halogen selected from Br and I, preferably Br.

20 Preferably, the reaction is carried out at a basic pH, for instance by adding an aqueous solution of a strong base, such as NaOH or KOH, or a tertiary amine, e.g. triethylamine, in a solvent comprising water and at least one at least partially water-soluble
25 organic solvent, which is able to solubilize at least

-7-

partially the fluorinated alcohol having formula (II).
Example of suitable organic solvents are: acetone,
N,N-dimethyl formamide, N-methyl pyrrolidone, tetrahy-
drofurane.

5 In order to promote the reaction between the
fluorinated alcohol having formula (II), which is at
least partially soluble in the aqueous medium, and the
alkyl halide having formula (III), which is basically
insoluble in the aqueous medium, the reaction mixture
10 is added with at least one phase transfer catalyst,
e.g. a quaternary ammonium salt, in particular a
tetraalkyl ammonium salt or a benzyltrialkyl ammonium
salt, e.g. benzyltriethyl ammonium chloride.

The reaction is preferably carried out at a tem-
15 perature of from 25°C to 100°C, preferably from 40°C
to 70°C, for a period of time generally of from 2 to
40 hours, preferably from 4 to 10 hours.

At the end of the reaction, after separating the
aqueous phase, the organic phase can be purified, e.g.
20 by distillation. In alternative or in addition to dis-
tillation, the end product can be purified by passage
in a chromatographic column containing, for instance,
silica or alumina.

According to a further aspect, the present inven-
25 tion relates to a mixture of at least one fluoroalky-

loxy alkane having formula (I) and at least one silicone oil.

Preferably, the aforesaid mixture comprises from 10% to 95% by weight, more preferably from 20% to 80%
5 by weight, of at least one fluoroalkyloxy alkane having formula (I), and from 5% to 90% by weight, more preferably from 20 to 80% by weight, of at least one silicone oil.

Preferably, said at least one silicone oil has a
10 viscosity of from 100 to 100,000 cS (centistokes), measured at 20°C. Preferably, said silicone oil is a polydimethylsiloxane.

According to a further aspect, the present invention relates to a fluoroalkyloxy alkane having formula
15 (I) for use as a medicament, in particular in ophthalmology.

According a further aspect, the present invention relates to a fluoroalkyloxy alkane having formula (I) for use as a tamponade liquid in an operation for the
20 treatment of retinal detachment.

According a further aspect, the present invention relates to a fluoroalkyloxy alkane having formula (I) for use as a vitreous body substitute. This use can be either permanent or temporary, usually for at least 12
25 months.

-9-

According a further aspect, the present invention relates to a fluoroalkyloxy alkane having formula (I) for use as an agent for oxygenating biological tissues.

5 According to a further aspect, the present invention relates to a fluoroalkyloxy alkane having formula (I) as a drug carrier.

 According to a further aspect, the present invention relates to a mixture of at least one fluoroalkyloxy alkane having formula (I) and at least one silicone oil for use as a medicament in ophthalmology.

10

 According to a further aspect, the present invention relates to a mixture of at least one fluoroalkyloxy alkane having formula (I) and at least one silicone oil for use as a tamponade liquid in an operation for the treatment of retinal detachment.

15

 According to a further aspect, the present invention relates to a mixture of at least one fluoroalkyloxy alkane having formula (I) and at least one silicone oil for use as a vitreous body substitute.

20

 According to a further aspect, the present invention relates to the use of a fluoroalkyloxy alkane having formula (I) for producing a medicament for use in ophthalmology.

25 According to a further aspect, the present inven-

-10-

tion relates to the use of a fluoroalkyloxy alkane having formula (I) for producing a tamponade liquid for use in an operation for the treatment of retinal detachment.

5 According to a further aspect, the present invention relates to the use of a fluoroalkyloxy alkane having formula (I) for producing a vitreous body substitute.

10 According to a further aspect, the present invention relates to the use of a mixture of at least one fluoroalkyloxy alkane having formula (I) and at least one silicone oil for producing a medicament for use in ophthalmology.

15 According to a further aspect, the present invention relates to the use of a mixture of at least one fluoroalkyloxy alkane having formula (I) and at least one silicone oil for producing a tamponade liquid for use in an operation for the treatment of retinal detachment.

20 According to a further aspect, the present invention relates to the use of a mixture of at least one fluoroalkyloxy alkane having formula (I) and at least one silicone oil for producing a vitreous body substitute.

25 The present invention will now be disclosed in

-11-

greater detail by way of some working examples, which are provided as mere non-limiting examples of the scope of the invention.

EXAMPLE 1

5 To a mixture, kept under stirring, of $C_6F_{13}CH_2CH_2OH$ (252 g, 0.692 moles), tetrahydrofurane (350 ml) and cyclohexane (300 ml) at 25°C, an aqueous solution of NaOH (400 ml, 50%) was added drop-wise. After stirring for 2 hours, benzyltriethyl ammonium chloride (25 g,
10 0.11 moles) as phase transfer catalyst, and then 1-bromopentane (209 g, 1.38 moles) were added. The reaction mixture was kept under stirring at 40°C for 40 hours, then at 70°C for 8 hours. The resulting mixture was poured into water and the organic phase thus ob-
15 tained was washed two times with water. After removing the fraction having a low boiling point, the raw product was subjected to distillation at reduced pressure, thus obtaining 215 g of $C_6F_{13}CH_2CH_2O(CH_2)_4CH_3$ (yield 72%, boiling point 110°C/6 mbar, n_D^{20} 1.3385). Spectro-
20 graphic data confirm the obtained structure: GC/MS m/z at 435 $(M+H)^+$, 377 $(M-CH_2CH_2CH_2CH_3)^+$, 71 $(-CH_2CH_2CH_2CH_2CH_3)^+$; for NMR data see Tables 1-2.

EXAMPLE 2

To a mixture, kept under stirring, of $C_6F_{13}CH_2CH_2OH$
25 (252 g, 0.687 moles), tetrahydrofurane (350 ml) and

-12-

cyclohexane (300 ml) at 25°C, an aqueous solution of NaOH (400 ml, 50%) was added drop-wise. After stirring for 2 hours, benzyltriethyl ammonium chloride (25 g, 0.11 moles) as phase transfer catalyst, and then 1-bromopropane (170 g, 1.38 moles) were added. The reaction mixture was kept under stirring at 40°C for 40 hours, then at 70°C for 8 hours. The resulting mixture was poured into water and the organic phase thus obtained was washed two times with water. After removing the fraction having a low boiling point, the raw product was treated with toluene 2,4-diisocyanate, in order to remove unreacted fluorinated alcohol, and then subjected to distillation at reduced pressure, thus obtaining 200 g of $C_6F_{13}CH_2CH_2O(CH_2)_2CH_3$ (yield 71%, boiling point 174°C, n_D^{20} 1.3245). Spectrographic data confirm the obtained structure: GC/MS m/z at 405 (M-H)⁺, 377 (M-CH₂CH₃)⁺, 73 (-CH₂OCH₂CH₂CH₃)⁺, 43 (-CH₂CH₂CH₃)⁺; for NMR data see Tables 1-2.

EXAMPLE 3

To a mixture, kept under stirring, of $C_4F_9CH_2CH_2OH$ (200 g, 0.757 moles), tetrahydrofuran (350 ml) and cyclohexane (300 ml) at 25°C, an aqueous solution of NaOH (400 ml, 50%) was added drop-wise. After stirring for 2 hours, benzyltriethyl ammonium chloride (25 g, 0.11 moles) as phase transfer catalyst, and then 1-

-13-

bromopentane (200 g, 1.32 moles) were added. The reaction mixture was kept under stirring at 40°C for 40 hours, then at 70°C for 8 hours. The resulting mixture was poured into water and the organic phase thus obtained was washed two times with water. After removing the fraction having a low boiling point, the raw product was subjected to distillation at reduced pressure, thus obtaining 200 g of $C_4F_9CH_2CH_2O(CH_2)_4CH_3$ (yield 79%, boiling point 183°C, n_D^{20} 1.3435). Spectrographic data confirm the obtained structure: GC/MS m/z at 335 $(M+H)^+$, 277 $(M-CH_2CH_2CH_2CH_3)^+$, 73 $(-CH_2OCH_2CH_2CH_3)^+$, 43 $(-CH_2CH_2CH_3)^+$; for NMR data see Tables 1-2.

EXAMPLE 4

To a mixture, kept under stirring, of $C_4F_9CH_2CH_2OH$ (200 g, 0.757 moles), tetrahydrofuran (350 ml) and cyclohexane (300 ml) at 25°C, an aqueous solution of NaOH (400 ml, 50%) was added drop-wise. After stirring for 2 hours, benzyltriethyl ammonium chloride (25 g, 0.11 moles) as phase transfer catalyst, and then 1-bromopropane (170 g, 1.38 moles) were added. The reaction mixture was kept under stirring at 40°C for 40 hours, then at 70°C for 8 hours. The resulting mixture was poured into water and the organic phase thus obtained was washed two times with water. After removing the fraction having a low boiling point, the raw prod-

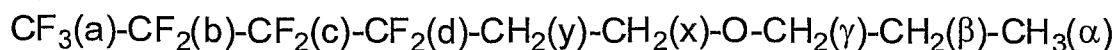
-14-

uct was subjected to distillation at reduced pressure, thus obtaining 200 g of $C_4F_9CH_2CH_2O(CH_2)_2CH_3$ (yield 86%, boiling temp. $147^\circ C$, n_D^{20} 1.3255). Spectrographic data confirm the obtained structure: GC/MS m/z at 305 (M-H)⁺, 377 (M-CH₂CH₃)⁺, 73 (-CH₂OCH₂CH₂CH₃)⁺, 43 (-CH₂CH₂CH₃)⁺; for NMR data see Tables 1-2.

EXAMPLE 5

The same fluoroalkyloxy alkanes as in Examples 1-4 were prepared following an alternative procedure. A mixture comprising 0.1 moles of fluorinated alcohol, 60 ml of N-methyl-2-pyrrolidone, 0.2 moles of 1-bromoalkane, and 60 ml of a 45% aqueous solution of KOH was heated under stirring for 5 hours at $50^\circ C$, then at $70^\circ C$ for 2 hours so as to complete the reaction. The raw reaction mixture was filtered so as to remove the formed KBr, and then diluted in 20 ml of water; the organic phase thus obtained comprised the desired fluoroalkyloxy alkane (yield: 80%).

As far as NMR data are concerned, these were obtained in acetone-d₆. Indexes identifying the various carbon atoms are assigned as disclosed above for the product $CF_3(CF_2)_3CH_2CH_2O(CH_2)_2CH_3$:



-15-

TABLE 1

 $(^{19}\text{F}$ NMR DATA)

Product	CF_3 (a)	CF_2 (b)	CF_2 (c)	CF_2 (d)	CF_2 (e)	CF_2 (f)
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	-84.2 t (3F)	-128.9 m (2F)	-127.3 m (2F)	-116.2 m (2F)	-	-
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	-84.2 t (3F)	-128.9 m (2F)	-127.4 m (2F)	-116.3 m (2F)	-	-
$\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	-83.9 t (3F)	-129.1 m (2F)	-126.3 m (2F)	-125.6 m (2F)	-124.6 m (2F)	-116.0 m (2F)
$\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	-84.0 t (3F)	-129.1 m (2F)	-126.4 m (2F)	-125.6 m (2F)	-124.6 m (2F)	-116.0 m (2F)

TABLE 2

 $(^1\text{H}$ NMR DATA)

Product	CH_3 (α)	CH_2 (β)	CH_2 (γ)	CH_2 (δ)	CH_2 (ϵ)	CH_2 (κ)	CH_2 (η)
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	0.90 t (3H)	1.56 tq (2H)	3.41 t (2H)	-	-	3.73 t (2H)	2.49 ttt (2H)
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	0.89 t (3H)	1.32 m (4H)		1.56 m (2H)	3.45 t (2H)	3.73 t (2H)	2.49 ttt (2H)
$\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	0.90 t (3H)	1.55 tq (2H)	3.42 t (2H)	-	-	3.74 t (2H)	2.50 ttt (2H)
$\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	0.90 t (3H)	1.35 m (4H)	1.33 m (2H)	1.57 m (2H)	3.46 t (2H)	3.73 t (2H)	2.48 ttt (3H)

5 EXAMPLE 6

Various mixtures comprising a fluoroalkyloxy alkane obtained according to Examples 1, 3 and 4 and a silicone oil having a viscosity of 1,000 cS (at 20°C) were prepared.

10 Table 3 contains the amounts of fluoroalkyloxy

-16-

alkane in the various mixtures (expressed as weight % on the total weight of the mixture), and the result in terms of clarity of the solution at different temperatures.

5

TABLE 3

Product	20%	33%	43%	50%	60%	90%
$\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	++	++	+	+	n.d.	n.d.
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	n.d.	++	++	++	++	++
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	n.d.	++	++	++	++	++

++: the mixture is clear after stirring at room temperature

10 +: the mixture is opalescent after stirring at room temperature, it becomes clear after heating at 37°C.

EXAMPLE 7

15 Various mixtures comprising a fluoroalkyloxy alkane obtained according to Examples 1, 3 and 4 and a silicone oil having a viscosity of 5,000 cS (at 20°C) were prepared.

20 Table 4 contains the amounts of fluoroalkyloxy alkane in the various mixtures (expressed as weight % on the total weight of the mixture), and the result in terms of clarity of the solution at different temperatures.

-17-

TABLE 4

Product	20%	33%	43%	50%	60%	90%
$\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	++	++	+	+	n.d.	n.d.
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	n.d.	++	++	++	++	++
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	n.d.	++	++	++	++	++

5 ++: the mixture is clear after stirring at room temperature

+: the mixture is opalescent after stirring at room temperature, it becomes clear after heating at 37°C.

EXAMPLE 8

10 The following mixtures (weight %) comprising the fluoroalkyloxy alkanes obtained according to Examples 3 and 4 with silicone oils having different viscosity values were prepared:

TABLE 5

	Mixture 1	Mixture 2	Mixture 3	Mixture 4
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_4\text{CH}_3$	90	90	--	--
$\text{CF}_3(\text{CF}_2)_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_2\text{CH}_3$	--	--	90	90
Silicone oil 1,000 cS (20°C)	10	--	10	--
Silicone oil 5,000 cS (20°C)	--	10	--	10

-18-

The aforesaid mixtures were cooled at 4°C. After cooling, Mixtures 1-3 remained perfectly clear, whereas Mixture 4 showed a phase separation; after stirring opalescence was observed; after being brought
5 to room temperature, Mixture 4 became clear after stirring.

These tests show the high solubility of fluoroalkyloxy alkanes according to the present invention with silicone oils in a wide range of concentrations, temperature and viscosity of said oils.
10

-19-

CLAIMS

1. Fluoroalkyloxy alkanes having formula (I):



wherein:

5 R_F is a linear or branched perfluoroalkyl group, having from 1 to 12, preferably from 2 to 8, carbon atoms;

R_1 is a linear or branched, non-fluorinated alkylene group, having from 1 to 6, preferably from 2 to 4,
10 carbon atoms;

R_2 is a linear or branched, non-fluorinated alkyl group, having from 1 to 12, preferably from 2 to 8, carbon atoms, possibly containing at least one ether bond -O- along the chain.

15 2. The fluoroalkyloxy alkanes according to claim 1, wherein R_F is a linear or branched perfluoroalkyl group having formula $CF_3(CF_2)_n-$, wherein n is an integer from 1 to 12, more preferably from 2 to 8.

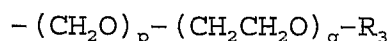
3. The fluoroalkyloxy alkanes according to any
20 of the preceding claims, wherein R_1 is a linear alkylene group having formula $-(CH_2)_r-$, wherein r is an integer from 1 to 6, preferably from 2 to 4.

4. The fluoroalkyloxy alkanes according to any
of the preceding claims, wherein R_2 is a linear, non-
25 fluorinated alkyl group having formula $CH_3(CH_2)_m-$,

-20-

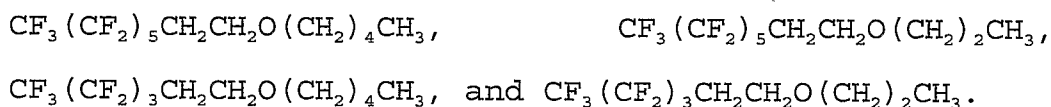
wherein m is an integer from 1 to 12, more preferably from 2 to 8.

5 5. The fluoroalkyloxy alkanes according to any of the claims 1 to 3, wherein R_2 is a group having formula:



wherein: R_3 is $-CH_3$ or $-C_2H_5$; p is zero or an integer from 1 to 4; q is an integer from 1 to 4; the $-CH_2O-$ and $-CH_2CH_2O-$ groups being statistically distributed
10 along the chain.

6. The fluoroalkyloxy alkanes according to claim 1, selected from:



15 7. The fluoroalkyloxy alkanes according to any of the preceding claims, having a density of from 1.2 to 1.5 g/cm³, measured at 20°C.

8. A process for preparing a fluoroalkyloxy alkane having formula (I) according to any of the preceding claims, comprising reacting a fluorinated alcohol having formula (II):



wherein R_F and R_1 are as defined above, with an alkyl halide having formula (III):



-21-

wherein R_2 is as defined above and X is a halogen selected from Br and I, preferably Br.

9. The process according to claim 8, wherein the reaction is carried out at a basic pH in a solvent comprising water and at least one at least partially water-soluble organic solvent.

10. The process according to claim 8 or 9, further comprising adding to the reaction mixture at least one phase transfer catalyst.

11. The process according to any of the claims from 8 to 10, wherein the reaction is carried out at a temperature of 25°C to 100°C, preferably of 40°C to 70°C, for a period of time generally of from 2 to 40 hours, preferably from 4 to 10 hours.

12. A mixture of at least one fluoroalkyloxy alkane having formula (I) according to any of the claims 1 to 7 and at least one silicone oil.

13. The mixture according to claim 12, comprising from 10% to 95% by weight, preferably from 20% to 80% by weight, of at least one fluoroalkyloxy alkane having formula (I), and from 5% to 90% by weight, preferably from 20% to 80% by weight, of at least one silicone oil.

14. The mixture according to claim 12 or 13, wherein said at least one silicone oil has a viscosity

-22-

of from 100 to 100,000 cS (centistokes), measured at 20°C.

15 15. A fluoroalkyloxy alkane having formula (I) according to any of the claims from 1 to 8 for use as a medicament, in particular in ophthalmology.

16. The fluoroalkyloxy alkane having formula (I) according to any of the claims from 1 to 7 for use as a tamponade liquid in an operation for the treatment of retinal detachment.

10 17. The fluoroalkyloxy alkane having formula (I) according to any of the claims from 1 to 7 for use as a vitreous body substitute.

15 18. The fluoroalkyloxy alkane having formula (I) according to any of the claims from 1 to 7 for use as an agent for oxygenating biological tissues.

19. The fluoroalkyloxy alkane having formula (I) according to any of the claims from 1 to 7 for use as a drug carrier.

20 20. The mixture according to any of the claims from 12 to 14 for use as a medicament in ophthalmology.

21. The mixture according to any of the claims from 12 to 14 for use as a tamponade liquid in an operation for the treatment of retinal detachment.

25 22. The mixture according to any of the claims

-23-

from 12 to 14 for use as a vitreous body substitute.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IT2008/000293

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07C41/16 C07C43/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 060 626 A (FUJII YASUYUKI [JP] ET AL) 9 May 2000 (2000-05-09) abstract; column 10, lines 45-55 - column 1, lines 60-67; table 2	1-4, 12, 13, 18, 19
X	WO 02/03958 A (ASTRAZENECA AB [SE]; ROGUEDA PHILIPPE [GB]) 17 January 2002 (2002-01-17)	1-4, 15, 18, 19
Y	page 2, lines 18-28; claims 1, 8	1-22
X	C. H. DEPUY, S. GRONERT, A. MULLIN, V. M. BIERBAUM: "Gas-phase SN2 and E2 reactions of alkyl halides" J. AM. CHEM. SOC., vol. 112, 1990, page 8650-8655, XP002517121 abstract; table V	1-4, 8
-/--		



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

27 February 2009

Date of mailing of the international search report

17/03/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer

Steinreiber, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/IT2008/000293

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SELVE CLAUDE ET AL: "Synthesis of monodisperse perfluoroalkyl oxyethylene surfactants with methoxy capping: surfactants of high chemical inertness" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, CHEMICAL SOCIETY, LETCHWORTH, GB, 1 January 1990 (1990-01-01), pages 911-912, XP009112323 ISSN: 0022-4936	1-3,5
Y	page 912; table 1	1-22
X	M. B. SMITH, J. MARCH: "March's Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, 5th Edition" 2001, WILEY-INTERSCIENCE, NEW YORK, USA, ISBN 0-471-58589-0, XP002517122 chapter 10-12 page 477	8-11
X	CHU ET AL: "New fluoruous/organic biphasic systems achieved by solvent tuning" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 63, no. 39, 16 August 2007 (2007-08-16), pages 9890-9895, XP022201081 ISSN: 0040-4020	1-3,7
Y	pages 9890-91; table 1	1-22
X	JP 10 175899 A (KAO CORP) 30 June 1998 (1998-06-30) paragraph [0042]	1,3,4
X	WO 96/40834 A (DU PONT [US]) 19 December 1996 (1996-12-19)	1-4,7
Y	page 5, lines 13,14; table 1	1-22
X	WO 97/39081 A (DU PONT [US]) 23 October 1997 (1997-10-23) page 1, line 5 - line 14; claim 2	1-4,15
Y	WO 2005/117850 A (UNIV COLUMBIA [US]; CHANG STANLEY [US]; SIMPSON RODERIC NIGEL FRASER []) 15 December 2005 (2005-12-15) cited in the application abstract; paragraphs [0006], [0050]; table 1	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IT2008/000293

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6060626	A	09-05-2000	DE 19816938 A1	22-04-1999
WO 0203958	A	17-01-2002	AT 342048 T	15-11-2006
			AU 7286601 A	21-01-2002
			AU 2001272866 B2	11-08-2005
			BR 0112322 A	08-07-2003
			CA 2415092 A1	17-01-2002
			CN 1455663 A	12-11-2003
			DE 60123793 T2	06-09-2007
			DK 1303258 T3	22-01-2007
			EP 1303258 A1	23-04-2003
			ES 2273864 T3	16-05-2007
			JP 2004502719 T	29-01-2004
			MX PA03000276 A	06-06-2003
			NO 20030133 A	24-02-2003
			NZ 523379 A	25-06-2004
			US 2003194378 A1	16-10-2003
			ZA 200300075 A	05-04-2004
JP 10175899	A	30-06-1998	JP 3304829 B2	22-07-2002
WO 9640834	A	19-12-1996	EP 0830436 A1	25-03-1998
			JP 10506926 T	07-07-1998
WO 9739081	A	23-10-1997	US 5730894 A	24-03-1998
WO 2005117850	A	15-12-2005	AU 2005249497 A1	15-12-2005
			CA 2568616 A1	15-12-2005
			EP 1758567 A1	07-03-2007
			JP 2008501032 T	17-01-2008