

Semifluorinated symmetrical diethers*

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Abstract

Semifluorinated unbranched symmetrical diethers have been synthesized via the Williamson ether synthesis and their chemical and physical properties investigated. They are remarkably inert compounds, being resistant to nucleophiles, oxidizers and mineral acids. Their oxygen solubility is similar to that of perfluorocarbons although their density is significantly lower.

Semifluorinated diethers with long hydrocarbon spacers and long R_F tails can be used for solubilizing hydrocarbons and perfluorocarbons. Diethers with short hydrocarbon spacers and long R_F tails can replace perfluorocarbons in perfluorocarbon emulsions.

Introduction

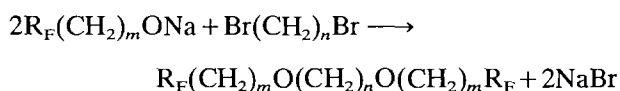
Perfluorocarbons are chemically inert compounds of high oxygen solubility. They are of medical interest since they exhibit neither catabolism nor metabolism in the human body [1]. The development of perfluorocarbons as oxygen-carriers commenced some 30 years ago [2] and recently they have been used in ophthalmology for flattening the retina in the case of retinal detachment [3, 4]. However, in this latter application the high density of perfluorocarbons is suggested as damaging the choroidal tissue [5]. For this reason, we have developed compounds with similar properties to perfluorocarbons but with a lower density. In order to lower the density in a controlled manner, hydrocarbon spacers of different length have been inserted between the two perfluorinated terminal groups.

Semifluorinated symmetrical unbranched diethers of the type CF₃(CF₂)_mCH₂O(CH₂)_nOCH₂(CF₂)_mCF₃ have been described only a few times in the literature [6, 7]. No reference appears to have been made to the synthesis of semifluorinated unbranched symmetrical diethers of the type CF₃(CF₂)_mCH₂CH₂O(CH₂)_nOCH₂CH₂(CF₂)_mCF₃.

Results and discussion

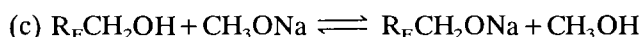
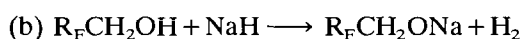
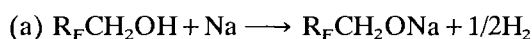
Semifluorinated diethers were prepared by the Williamson ether synthesis using semifluorinated alcohol-

ates and alkyl dihalides as starting materials.



Side products were not observed in these reactions except that perfluoroalkylethyl alcoholates formed one byproduct which has yet to be identified. The 1-haloalkyl perfluoroalkyl ether formed as an intermediate was completely transformed to the diether. The reaction time appears to depend on the chain length of R_F and that of the alkyl dihalide decreasing with increasing hydrocarbon chain length and increasing with increasing length of the R_F chain. The reverse reaction of perfluoroalkylethyl halides and the corresponding α,ω-dialcoholates was not expected.

Semifluorinated alcoholate anions may be prepared according to:



The following points should be noted:

(1) The alcoholate of trifluoroethanol may be synthesized by the reaction of metallic sodium at 60 °C, using excess trifluoroethanol as the solvent. However, use of the same reaction for synthesizing alcoholates with longer R_F chains led to the formation of sodium fluoride and an unidentified polymeric product in a strongly exothermic reaction.

(2) If sodium hydride is employed instead of metallic sodium, the alcoholate can still be synthesized as above

*This work is dedicated to Professor Dr W. Sawodny on the occasion of his 60th birthday.

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TABLE 1. Diethers synthesized in the present work

Diether	d^{21} (g cm ⁻³)	n_D^{37}	B.p. (°C/mmHg)	Yield (%)
I (CF₃CH₂O)₂(CH₂)_n				
1. (a) $n=3$	1.23	1.3280	152/760	78
2. (a) $n=4$	1.21	1.3395	76/16	78
3. (a) $n=5$	1.18	1.3481	92/15	79
4. (a) $n=6$	1.16	1.3550	107/18	80
II (CF₃CF₂CH₂O)₂(CH₂)_n				
1. (c) $n=3$	1.40	1.3195	69/15	68
2. (c) $n=4$	1.37	1.3290	82/14	69
3. (c) $n=5$	1.34	1.3340	96/12	70
4. (c) $n=6$	1.32	1.3410	110/14	69
III (CF₃(CF₂)₂CH₂O)₂(CH₂)_n				
1. (b) $n=3$	1.51	1.3140	92/18	68
2. (b) $n=4$	1.47	1.3215	104/15	69
3. (b) $n=5$	1.44	1.3285	118/16	68
4. (b) $n=6$	1.39	1.3340	133/18	70
IV (CF₃(CF₂)₃(CH₂)₂O)₂(CH₂)_n				
1. (b) $n=3$	1.45	1.3270	142/15	65
2. (b) $n=4$	1.41	1.3335	88/0.5	67
3. (c) $n=5$	1.38	1.3385	97/0.5	68
4. (c) $n=6$	1.34	1.3425	111/0.5	68
V (CF₃(CF₂)₅(CH₂)₂O)₂(CH₂)_n				
1. (c) $n=3$	1.55	1.3220	139/0.5	67
2. (c) $n=4$	1.51	1.3295	151/0.5	64
3. (b) $n=5$	1.48	1.3360	160/0.5	69
4. (b) $n=6$	1.44	1.3415	167/0.5	68

(reaction a), through the use of an excess of the corresponding semifluorinated alcohol as the solvent.

(3) The greater acidity of semifluorinated alcohols relative to hydrocarbon alcohols is useful when a semifluorinated alcohol is added to sodium methoxide (reaction c above). To displace the equilibrium, the methanol formed is removed by distillation. Excess of the corresponding semifluorinated alcohol is also used as the solvent in this case.

According to our results, the acidity of the semifluorinated alcohols used for the preparation of the diethers decreases with increasing R_F chain length. Apart from trifluoroethanol, 3,3,3,2,2-pentafluoro-1-propanol was the highest acidity alcohol used in the reactions studied, while formation of the corresponding sodium alcoholate was the most exothermic process involved.

Alcoholates can also be synthesized by phase-transfer catalysis using trioctylmethylammonium chloride (3–5 mol%) in a 40% aqueous solution of NaOH. However, this method gave low yields and increased reaction times.

The diethers synthesized in this work are listed in Table 1. The yields quoted are based on the amount of dibromoalkane employed, which extended from 65% to 80%, and are seen to depend strongly on the length

of the R_F tail. It will be seen that the yields decreased with increasing R_F chain length. The diethers listed as Group I were synthesized via metallic sodium (reaction a), whilst the others were either synthesized via sodium hydride (reaction b) or sodium methoxide (reaction c) as indicated in Table 1. All products were clear colourless liquids with refractive indices within the range 1.3195–1.3550.

TABLE 2. Interfacial tension of synthesized diethers against water at 21 °C

Diether	Interfacial tension (mN m ⁻¹)
(CF ₃ CH ₂ O) ₂ (CH ₂) ₃	25.7
(CF ₃ CH ₂ O) ₂ (CH ₂) ₄	24.5
(CF ₃ CH ₂ O) ₂ (CH ₂) ₅	23.5
(CF ₃ CH ₂ O) ₂ (CH ₂) ₆	22.4
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₃	28.5
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₄	26.6
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₅	24.7
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₆	23.3
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₃	29.2
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₄	27.1
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₅	24.8
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₆	23.5

TABLE 3. Oxygen solubility of synthesized diethers at 37 °C

Diether	Oxygen solubility (vol.%)
(CF ₃ CH ₂ O) ₂ (CH ₂) ₃	32.7
(CF ₃ CH ₂ O) ₂ (CH ₂) ₄	32.3
(CF ₃ CH ₂ O) ₂ (CH ₂) ₅	32.4
(CF ₃ CH ₂ O) ₂ (CH ₂) ₆	32.2
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₃	37.8
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₄	37.0
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₅	36.7
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₆	34.3
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₃	42.3
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₄	40.7
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₅	40.1
(CF ₃ CF ₂ CF ₂ CH ₂ O) ₂ (CH ₂) ₆	39.8

In order to examine their potential medical application, selected physical properties of the semifluorinated diethers were determined as discussed below.

Density

As stated above, the high density of perfluorocarbons is assumed to damage the choroidal tissue, the preferred density being less than 1.6 g cm⁻³. From Table 1, it will be seen that the density of the semifluorinated diethers is in the desired range of 1.1–1.6 g cm⁻³. The density decreases as the length of the hydrocarbon spacer increases.

Stability

Perfluorocarbons are very inert compounds. Because of the presence of vicinal CH₂ groups, the elimination of HF, the formation of toxic fluoro-olefins and hence

the generation of fluoride ions could be expected in the case of semifluorinated diethers. To check this point, the following tests were undertaken with these ethers: (i) their resistance towards strong bases was tested by contact with 8 N potassium hydroxide solution for 16 h at 120 °C; (ii) their resistance towards strong oxidizers was tested by contact with potassium permanganate (2 N) in acidic medium (1 N H₂SO₄) for 8 h at 70 °C; and (iii) their resistance against nucleophiles was tested with hexamethylenediamine (25%) in decane at 120 °C.

In no case was any reaction observed. Reaction mixtures were monitored by GC methods (column I) against perfluorodecalin. The possible formation of fluoride ions was investigated by means of a fluoride-sensitive electrode, but no fluoride was observed under any of the above conditions. For these reasons, it is safe to assume that there is no reaction between the CH₂ and CF₂ groups.

Interfacial tension

A high interfacial tension against water is necessary in ophthalmological applications. The interfacial tension of perfluorocarbons against water is similar to that of hydrocarbons, being *c.* 50 mN m⁻¹ [8]. The interfacial tension of semifluorinated diethers against water is lower but satisfactory for ophthalmological applications (Table 2). The interfacial tension of semifluorinated diethers increases with increasing fluorine content and decreases with increasing length of hydrocarbon spacer.

Oxygen solubility

Perfluorocarbons are well known as having a high solubility towards gases; for example, the oxygen

TABLE 4. Miscibility of synthesized diethers in various solvents

Diether	Solvent			
	Silicone oil, H ₂ O	Alcohols, short-chain alkanes	Long-chain alkanes	PFCs ^a
(CF ₃ CH ₂ O) ₂ (CH ₂) ₃	–	+	–	+
(CF ₃ CH ₂ O) ₂ (CH ₂) ₄	–	+	+	–
(CF ₃ CH ₂ O) ₂ (CH ₂) ₅	–	+	+	–
(CF ₃ CH ₂ O) ₂ (CH ₂) ₆	–	+	+	–
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₃	–	+	–	+
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₄	–	+	–	+
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₅	–	+	+	+
(CF ₃ CF ₂ CH ₂ O) ₂ (CH ₂) ₆	–	+	+	+
(CF ₃ (CF ₂) ₂ CH ₂ O) ₂ (CH ₂) ₃	–	+	–	+
(CF ₃ (CF ₂) ₂ CH ₂ O) ₂ (CH ₂) ₄	–	+	–	+
(CF ₃ (CF ₂) ₂ CH ₂ O) ₂ (CH ₂) ₅	–	+	–	+
(CF ₃ (CF ₂) ₂ CH ₂ O) ₂ (CH ₂) ₆	–	+	+	+

^aPerfluorodecalin, perfluoro-octane, perfluorotributylamine.

TABLE 5. Spectral data for synthesized diethers

$(CF_3CH_2O)_2(CH_2)_3$	1H NMR δ : 3.78 (q, $^3J_{H,F}=9$ Hz); 3.69 (t, $^3J_{H,H}=6$ Hz); 1.88 (m) ppm. MS m/z : 240 (M^+ , 13.8%); 220 ($M^+ - HF$, 68.8%); 140 ($M^+ - CF_3CH_2OH$, 100%).
$(CF_3CH_2O)_2(CH_2)_4$	1H NMR δ : 3.79 (q, $^3J_{H,F}=9$ Hz); 3.62 (O, $^3J_{H,H}=5$ Hz); 1.69 (m) ppm. MS m/z : 254 (M^+ , 100%); 234 ($M^+ - HF$, 6.4%); 154 ($M^+ - CF_3CH_2OH$, 2.9%).
$(CF_3CH_2O)_2(CH_2)_5$	1H NMR δ : 3.76 (q, $^3J_{H,F}=9$ Hz); 3.59 (t, $^3J_{H,H}=6$ Hz); 1.62 (m); 1.5 (m) ppm. MS m/z : 269 (M^+ , 4.1%); 248 ($M^+ - HF$, 15.7%); 168 ($M^+ - CF_3CH_2OH$, 100%); 68 ($M^+ - 2CF_3CH_2OH$, 27%).
$(CF_3CH_2O)_2(CH_2)_6$	1H NMR δ : 3.75 (q, $^3J_{H,F}=9$ Hz); 3.60 (t, $^3J_{H,H}=6$ Hz); 1.59 (m); 1.39 (m) ppm. MS m/z : 282 (M^+ , 46.8%); 262 ($M^+ - HF$, 79.2%); 182 ($M^+ - CF_3CH_2OH$, 100%); 82 ($M^+ - 2CF_3CH_2OH$, 38.7%).
$(CF_3CF_2CH_2O)_2(CH_2)_3$	1H NMR δ : 3.87 (t, $^3J_{H,F}=12$ Hz); 3.67 (t, $^3J_{H,H}=6$ Hz); 1.88 (m) ppm. MS m/z : 340 (M^+ , 11.1%); 320 ($M^+ - HF$, 100%); 190 ($M^+ - CF_3CF_2CH_2OH$, 76.9%).
$(CF_3CF_2CH_2O)_2(CH_2)_4$	1H NMR δ : 3.82 (t, $^3J_{H,F}=11$ Hz); 3.64 (t, $^3J_{H,H}=6$ Hz); 1.69 (m) ppm. MS m/z : 354 (M^+ , 100%).
$(CF_3CF_2CH_2O)_2(CH_2)_5$	1H NMR δ : 3.85 (t, $^3J_{H,F}=13$ Hz); 3.58 (t, $^3J_{H,H}=6$ Hz); 1.60 (m); 1.49 (m) ppm. MS m/z : 369 (MH^+ , 1.6%); 348 ($M^+ - HF$, 11.5%); 218 ($M^+ - CF_3CF_2CH_2OH$, 100%); 68 ($M^+ - 2CF_3CF_2CH_2OH$, 20.2%).
$(CF_3CF_2CH_2O)_2(CH_2)_6$	1H NMR δ : 3.86 (t, $^3J_{H,F}=12$ Hz); 3.58 (t, $^3J_{H,H}=6$ Hz); 1.59 (m); 1.38 (m) ppm. MS m/z : 382 (M^+ , 62.6%); 362 ($M^+ - HF$, 42.2%); 232 ($M^+ - CF_3CF_2CH_2OH$, 100%); 82 ($M^+ - 2CF_3CF_2CH_2OH$, 23.9%).
$(CF_3(CF_2)_2CH_2O)_2(CH_2)_3$	1H NMR δ : 3.91 (t, $^3J_{H,F}=11$ Hz); 3.69 (t, $^3J_{H,H}=6$ Hz); 1.89 (m) ppm. MS m/z : 441 (MH^+ , 11.6%); 420 ($M^+ - HF$, 100%).
$(CF_3(CF_2)_2CH_2O)_2(CH_2)_4$	1H NMR δ : 3.90 (t, $^3J_{H,F}=11$ Hz); 3.62 (t, $^3J_{H,H}=6$ Hz); 1.70 (m) ppm. MS m/z : 454 (M^+ , 100%); 434 ($M^+ - HF$, 1.2%).
$(CF_3(CF_2)_2CH_2O)_2(CH_2)_5$	1H NMR δ : 3.90 (t, $^3J_{H,F}=11$ Hz); 3.59 (t, $^3J_{H,H}=6$ Hz); 1.63 (m); 1.45 (m) ppm. MS m/z : 468 (M^+ , 3.8%); 268 ($M^+ - CF_3(CF_2)_2CH_2OH$, 100%); 68 ($M^+ - 2CF_3(CF_2)_2CH_2OH$, 22.3%).
$(CF_3(CF_2)_2CH_2O)_2(CH_2)_6$	1H NMR δ : 3.90 (t, $^3J_{H,F}=14$ Hz); 3.59 (t, $^3J_{H,H}=6$ Hz); 1.61 (m); 1.38 (m) ppm. MS m/z : 482 (M^+ , 100%); 462 ($M^+ - HF$, 54.7%).
$(CF_3(CF_2)_3(CH_2)_2O)_2(CH_2)_3$	1H NMR δ : 3.71 (t, $^3J_{H,H}=7$ Hz); 3.54 (t, $^3J_{H,H}=6$ Hz); 2.38 (m); 1.84 (m) ppm. MS m/z : 568 (M^+ , 10.7%); 548 ($M^+ - HF$, 100%).
$(CF_3(CF_2)_3(CH_2)_2O)_2(CH_2)_4$	1H NMR δ : 3.70 (t, $^3J_{H,H}=7$ Hz); 3.47 (t, $^3J_{H,H}=6$ Hz); 2.38 (m); 1.64 (m) ppm. MS m/z : 582 (M^+ , 100%); 562 ($M^+ - HF$, 4.6%).

(continued)

TABLE 5. (continued)

$(CF_3(CF_2)_3(CH_2)_2O)_2(CH_2)_5$	1H NMR δ : 3.70 (t, $^3J_{H,H}=7$ Hz); 3.45 (t, $^3J_{H,H}=6$ Hz); 2.39 (m); 1.60 (m); 1.42 (m) ppm. MS m/z : 596 (M^+ , 100%); 576 ($M^+ - HF$, 21.1%); 332 ($M^+ - CF_3(CF_2)_3(CH_2)_2OH$, 15.6%).
$(CF_3(CF_2)_3(CH_2)_2O)_2(CH_2)_6$	1H NMR δ : 3.69 (t, $^3J_{H,H}=7$ Hz); 3.44 (t, $^3J_{H,H}=6$ Hz); 2.39 (m); 1.59 (m); 1.38 (m) ppm. MS m/z : 610 (M^+ , 100%); 590 ($M^+ - HF$, 43.8%).
$(CF_3(CF_2)_5(CH_2)_2O)_2(CH_2)_3$	1H NMR δ : 3.71 (t, $^3J_{H,H}=7$ Hz); 3.53 (t, $^3J_{H,H}=6$ Hz); 2.38 (m); 1.84 (m) ppm.
$(CF_3(CF_2)_5(CH_2)_2O)_2(CH_2)_4$	1H NMR δ : 3.70 (t, $^3J_{H,H}=7$ Hz); 3.47 (t, $^3J_{H,H}=6$ Hz); 2.38 (m); 1.65 (m) ppm.
$(CF_3(CF_2)_5(CH_2)_2O)_2(CH_2)_5$	1H NMR δ : 3.69 (t, $^3J_{H,H}=7$ Hz); 3.45 (t, $^3J_{H,H}=6$ Hz); 2.38 (m); 1.60 (m); 1.44 (m) ppm.
$(CF_3(CF_2)_5(CH_2)_2O)_2(CH_2)_6$	1H NMR δ : 3.69 (t, $^3J_{H,H}=7$ Hz); 3.45 (t, $^3J_{H,H}=6$ Hz); 2.37 (m); 1.59 (m); 1.39 (m) ppm.

solubility in perfluorodecalin reaches values as high as 45 vol. % [9]. The oxygen solubility of the semifluorinated diethers has been examined by gas chromatography (column II) [10]. The oxygen solubility of some semifluorinated diethers is listed in Table 3. As the R_F chain increases, the oxygen solubility increases strongly and reaches the same order of magnitude as for perfluorocarbons.

Miscibility

To examine the possibility of introducing drugs into the vitreous and in the region of the retina, the miscibility of semifluorinated diethers with lipophilic and hydrophilic substances has been tested (Table 4). The diethers are immiscible with water and silicone oil but are miscible with alcohols and short-chain hydrocarbons. With increasing length of the R_F chain, the diethers become miscible with cyclic and acyclic perfluorocarbons. With a decreasing length of hydrocarbon spacer and a longer R_F tail, the diethers become immiscible with long-chain hydrocarbons.

With decreasing R_F chain length and an increasing length of hydrocarbon spacer, the diethers become miscible with long-chain hydrocarbons and immiscible with perfluorocarbons. Diethers with a high content of fluorine and long hydrocarbon spacers are miscible with cyclic and acyclic perfluorocarbons as well as with long-chain hydrocarbons. Hence, lipophilic drugs can be introduced by diethers. Diethers also provide ideal solubilizers for perfluorocarbons in a lipophilic medium. Diethers with short hydrocarbon spacers and long R_F chains which are immiscible in long-chain alkanes may have application as oxygen carriers in biological systems and for other purposes.

Experimental

General methods for the preparation of semifluorinated diethers

Reaction a

CF_3CH_2OH (0.6 mol) was added dropwise to metallic sodium (0.6 mol) at such a rate that the reaction temperature did not exceed 60 °C. (An excess of c. 20% CF_3CH_2OH was used as solvent.) The reaction mixture was refluxed for 2 h, then α,ω -dibromoalkane (0.3 mol) was added dropwise. After refluxing the solution for 20 h under N_2 , 200 ml of a 5% aqueous solution of NaOH was added. The product was extracted with diethyl ether (200 ml) and dried (anhydrous Na_2SO_4). After removing the solvent, the liquid residue was fractionally distilled.

Reaction b

$CF_3(CF_2)_n(CH_2)_mOH$ (0.6 mol) was added dropwise under N_2 on to NaH (0.6 mol) at such a rate that the reaction temperature did not exceed 60 °C. (An excess of c. 20% $CF_3(CF_2)_n(CH_2)_mOH$ was used as solvent.) The reaction mixture was stirred for 5 h at 80 °C, then α,ω -dibromoalkane (0.3 mol) was added dropwise. After refluxing the solution for 20 h under N_2 , 200 ml of a 5% aqueous solution of NaOH was added. The product was extracted with diethyl ether (200 ml) and dried (anhydrous Na_2SO_4). After removing the solvent, the liquid residue was fractionally distilled.

Reaction c

$CF_3(CF_2)_n(CH_2)_mOH$ (0.6 mol) was added dropwise under N_2 on to CH_3ONa (0.6 mol) at such a rate that the reaction temperature did not exceed 60 °C. (An excess of c. 20% $CF_3(CF_2)_n(CH_2)_mOH$ was used as solvent.)

The reaction mixture was stirred for 5 h at 60 °C, and then CH₃OH was removed by distillation. After adding 0.3 mol of α,ω -dibromoalkane, the reaction mixture was stirred for 20 h at 90 °C under N₂. At this point, 200 ml of a 5% aqueous solution of NaOH was added, the product was extracted with diethyl ether (200 ml) and dried (anhydrous Na₂SO₄). After removing the solvent, the liquid residue was fractionally distilled.

Other procedures

Gas chromatography was carried out on a Gira CAP 12 gas chromatograph equipped with a thermal conductivity detector, using columns I and II for analytical separations. Column I: copper column (5 m × 4 mm i.d.) packed with 10% SE 30 on 80–100 mesh Chromosorb P. Column II: glass column (1.7 m × 3 mm i.d.) packed with 40–60 mesh 5 Å molecular sieve.

Interfacial tensions were measured on a K 8 tensiometer (Fa. Krüss) [11]. Results were corrected by the method of Zuidema and Waters [12]. ¹H NMR spectra were obtained on a Bruker MSL 300 instrument at 300.13 MHz (δ in ppm from TMS). Mass spectra were recorded on a Varian MAT 711 instrument at 8 kV using the field ionization technique. NMR and mass spectral results are recorded in Table 5.

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References

- 1 H. Meinert, R. Fackler, A. Knoblich, J. Mader, P. Reuter and W. Röhlke, *Biomat., Art. Cells Immobil. Biotechnol.*, **20** (1992) 95.
- 2 L.C. Clark and F. Gollan, *Science*, **152** (1966) 1755.
- 3 H. Meinert, *J. Vitreoretina*, **1** (1992) 5.
- 4 H. Meinert and U. Geister, *J. Vitreoretina*, **1** (1992) 31.
- 5 M. Winter, C. Eckardt and B. Havsteen, *J. Vitreoretina*, **1** (1992) 20.
- 6 E.J.P. Fear, J. Thrower and J. Veitch, *J. Chem. Soc.*, (1958) 1322.
- 7 V. Weinmayr, *J. Org. Chem.*, **28** (1963) 492.
- 8 K.L. Wolf, *Physik und Chemie der Grenzflächen*, Springer Verlag, Berlin, Vol. 2, 1959.
- 9 K. Yokoyama, K. Yamanouchi and T. Suyama, *Life Chem. Rep.*, **2** (1983) 35.
- 10 H. Meinert and J. Mader, in W. Günther (ed.), *Industrialized Analytical Chemistry and Computer Technology*, Vogel Verlag, Würzburg, 1992.
- 11 P. Lecomte du Noüy, *J. Gen. Physiol.*, **7** (1925) 525.
- 12 H.H. Zuidema and G.W. Waters, *Ind. Eng. Chem.*, **13** (1941) 312.