

## EUROPEAN QUALIFYING EXAMINATION 2012

# Paper A(Ch)

## Chemistry

This paper comprises:

- |   |                           |                     |
|---|---------------------------|---------------------|
| * | Letter from the applicant | 2012/A(Ch)/EN/1-8   |
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| * | Document D2               | 2012/A(Ch)/EN/11-16 |



**LETTER FROM THE APPLICANT**

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**[001]** We are a research institute specialised in the field of cosmetics. In the last few months, our research interests have focussed on the development of new UV filters. We have now discovered a new class of compounds which we think is worth patenting.

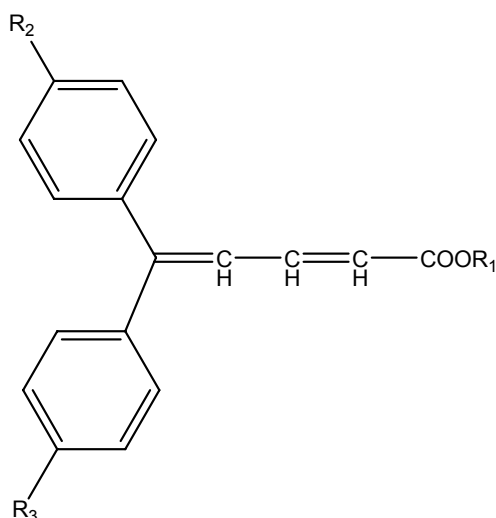
**[002]** Sunscreens are cosmetic compositions that absorb UV radiation. This is commonly achieved by a combination of UV-A and UV-B filters. However, a known problem with conventional sunscreens is that the filters interact with each other. This renders the sunscreen compositions unstable with the result that their protective properties are considerably diminished over time.

**[003]** In recent years, research has been carried out into UV-filters with improved stability. In this respect, the substitution with hydrophilic groups in known UV-filter compounds resulted in more stable sunscreens. Such compounds are soluble in water and, as a result, are easily removed from the skin during bathing or perspiration.

**[004]** We have now identified a new class of organic compounds which absorb UV-A radiation strongly. Contrary to most UV-A filters, the compounds of formula (I) provide good stability when used in combination with UV-B filters.



**[005]** These compounds are 4,4-diarylbutadiene derivatives of formula (I):



wherein

$R_1$  represents alkyl, cycloalkyl or phenyl, and

$R_2$  and  $R_3$  independently from each other represent H, alkyl, halogen,  $\text{Si}(\text{CH}_3)_3$ , OH or  $\text{NH}_2$ .

**[006]** We found that compounds in which  $R_1$  is a higher alkyl (e.g.  $R_1$  is heptyl ( $\text{C}_7\text{H}_{15}$ ), octyl ( $\text{C}_8\text{H}_{17}$ ) or decyl ( $\text{C}_{10}\text{H}_{21}$ )) are oily liquids which are very resistant to removal by fresh or sea water.

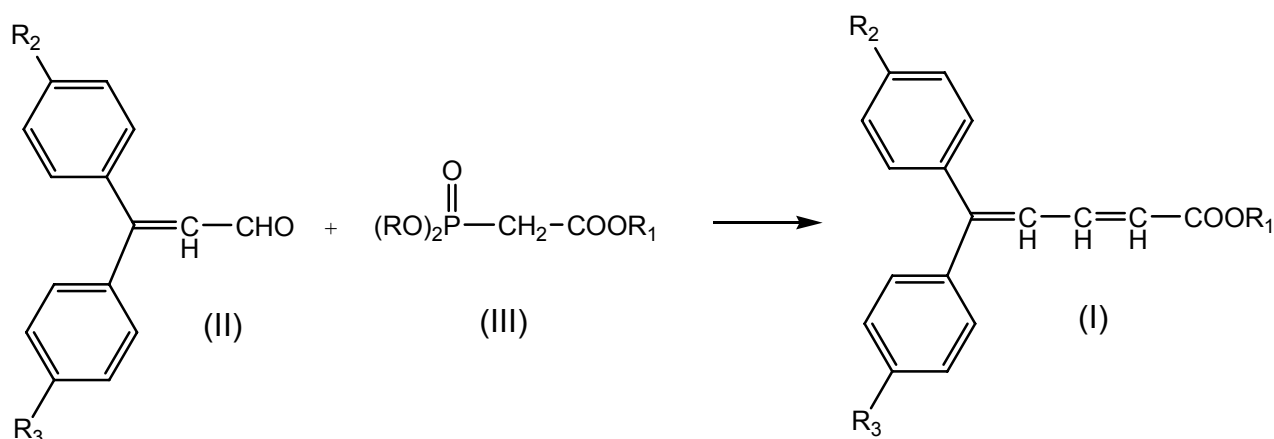
**[007]** The term “alkyl” refers to a straight or branched hydrocarbon group containing from 1 to 20, preferably from 1 to 10, carbon atoms. The term “higher alkyl” refers to alkyl groups containing at least 6 carbon atoms (e.g. hexyl, heptyl, octyl or decyl).

**[008]** The term “cycloalkyl” refers to a saturated monocyclic hydrocarbon group containing from 3 to 10, preferably from 3 to 6, carbon atoms. Examples of such groups include cyclopropyl, cyclopentyl and cyclohexyl.

**[009]** Compounds wherein both  $R_2$  and  $R_3$  are  $\text{Si}(\text{CH}_3)_3$  are particularly preferred.

**[010]** The compounds of formula (I) can be prepared by reacting a compound of formula (II) with a compound of formula (III) wherein R is  $\text{C}_1$ - $\text{C}_{10}$ -alkyl or phenyl.





**[011]** The compounds of formulae (II) and (III) are either commercially available or are readily made by known methods. The reaction is carried out in the presence of a base such as NaH, NaOH or LiOH. Preferred solvents for this reaction are alcohols such as ethanol, ethers such as diethyl ether, or aromatic hydrocarbons such as toluene. The reaction temperatures preferably employed are from 0°C to 150°C, in particular from 10°C to 100°C, particularly preferably from 20°C to 80°C. The compound of formula (III) is first mixed with the solvent at 0°C before the base is added. The compound of formula (II) is then slowly added and the reaction mixture is stirred for one to two hours at room temperature. The compound of formula (I) is extracted in a conventional manner. The use of ethers as the solvent and/or LiOH as the base leads to higher yields.

**[012]** The compounds of formula (I) are used in sunscreen compositions in an amount of from 0.01 to 20 wt. %, preferably from 0.1 to 10 wt. %, relative to the total weight of the composition. The sunscreen composition must contain at least one oil phase. Accordingly, oils or oil-in-water and water-in-oil emulsions are suitable. These emulsions may be in the form of creams, milks or gels. Water-in-oil emulsions are preferred. Though this type of composition has a more greasy feeling, it leaves a more resistant film on the skin. When emulsions are used, the presence of an emulsifier is required. Particularly effective emulsifiers are selected from sesquioleates, ethoxylated esters and polysiloxanes (e.g. cetyl dimethicone copolyol). The emulsifier generally represents from 0.5 to 20 wt. %, preferably from 2 to 10 wt. %, relative to the total weight of the composition.

**[013]** Esters or triglycerides are typically employed as the oil phase, in particular triglycerides of C<sub>8</sub>-C<sub>12</sub> fatty acids (such as "Miglyol 812"). The compositions must also comprise further additives such as stabilizers, thickeners and preservatives. The total content of additives varies from 1 to 80 wt. %, preferably from 10 to 30 wt. %, relative to the total weight of the composition. Typical examples of stabilizers that can be employed are metal salts of fatty acids such as magnesium stearate, aluminium stearate or zinc stearate. Examples of conventional thickeners are crosslinked polyacrylic acids, polysaccharides, in particular xanthan gum and guar gum, fatty alcohols (e.g. cetyl alcohol), polyacrylates and polyvinylpyrrolidone. Suitable preservatives are chosen from formaldehyde solution, EDTA derivatives or parabens such as methylparaben or propylparaben.

**[014]** A typical sunscreen has the following composition:

|                          |                  |
|--------------------------|------------------|
| UV filter of formula (I) | 2 - 7 wt. %      |
| UV-B filter              | 2 - 7 wt. %      |
| Preservative             | 0.05 - 1.0 wt. % |
| Emulsifier               | 4 - 8 wt. %      |
| Thickener                | 0.1 - 2 wt. %    |
| Oil phase                | 40 - 60 wt. %    |
| Water                    | 15 - 51.85 wt. % |

**[015]** The compositions can be produced by dissolving the compounds of formula (I) into the oil phase, adding the additives, heating, and, finally, adding the water with rapid stirring.

**[016]** The compositions may also comprise other UV-A filters and/or UV-B filters chosen from salicylic acid, camphor, benzophenone or p-aminobenzoic acid (PABA). The addition of a UV-B filter provides total absorbance of UV radiation.



**[017]** Our invention is illustrated by the following examples:

**[018]** Example 1:

Synthesis of compounds of formula (I)

Lithium hydroxide (LiOH) was added to the compound of formula (III) (10 mmol, R = phenyl) in 50 ml diethyl ether cooled to 0°C. The mixture was stirred for 15 minutes. The compound of formula (II) (10 mmol) in 10 ml ether was added drop-wise. The resulting reaction mixture was stirred at room temperature for 1 hour, and 100 ml of 0.1 M hydrochloric acid were added. The aqueous phase was extracted with diethyl ether. The organic phase was concentrated and the residue was purified by silica column chromatography to give the compound of formula (I).

**[019]** Compounds (1) to (11) tested below were made by this method.

**[020]** Example 2:

The compounds were tested for their photostability and their solubility in oil. Their absorbance was also determined.

**[021]** Photostability tests

A 3 % solution in Miglyol 812 of the compound to analyse was prepared and irradiated with a xenon arc solar simulator for 12 hours. After the irradiation period, the samples were analysed by comparison of the absorption spectra before and after exposure. A spectrophotometer was used for determining the absorbance. The results are indicated in percentage of product which remains unchanged. A result of at least 90% is an indication that the compounds are suitable for being used in sunscreen compositions without significant degradation.

**[022]** Solubility tests

The test compound was added drop-wise under stirring to 10 ml of castor oil until an additional phase appeared. The compounds were classified as soluble (S), poorly soluble (PS) or insoluble (IS).



**[023]** Measure of the absorbance

A solution containing the compound of formula (I) in Miglyol 812 was applied to a quartz plate. UV absorption spectra were recorded on a spectrophotometer. The results are given in terms of  $\lambda_{\max}$ , which is the wavelength at which maximum absorbance in the absorption spectrum is observed.

All the compounds absorb in the UV-A region, i.e. between 320 nm and 400 nm.

**[024]** Table 1

| Compound  | R <sub>1</sub>                  | R <sub>2</sub>                    | R <sub>3</sub>                    | $\lambda_{\max}$ in nm | Stability in % | Solubility |
|-----------|---------------------------------|-----------------------------------|-----------------------------------|------------------------|----------------|------------|
| <b>1</b>  | C <sub>5</sub> H <sub>11</sub>  | F                                 | OH                                | 359                    | 66             | PS         |
| <b>2</b>  | C <sub>7</sub> H <sub>15</sub>  | Si(CH <sub>3</sub> ) <sub>3</sub> | Si(CH <sub>3</sub> ) <sub>3</sub> | 340                    | 98             | S          |
| <b>3</b>  | C <sub>8</sub> H <sub>17</sub>  | C <sub>2</sub> H <sub>5</sub>     | Si(CH <sub>3</sub> ) <sub>3</sub> | 335                    | 97             | S          |
| <b>4</b>  | phenyl                          | F                                 | Si(CH <sub>3</sub> ) <sub>3</sub> | 356                    | 90             | S          |
| <b>5</b>  | cyclohexyl                      | Si(CH <sub>3</sub> ) <sub>3</sub> | CH <sub>3</sub>                   | 376                    | 95             | S          |
| <b>6</b>  | C <sub>10</sub> H <sub>21</sub> | Cl                                | Si(CH <sub>3</sub> ) <sub>3</sub> | 339                    | 92             | S          |
| <b>7</b>  | C <sub>8</sub> H <sub>17</sub>  | OH                                | NH <sub>2</sub>                   | 325                    | 30             | IS         |
| <b>8</b>  | C <sub>2</sub> H <sub>5</sub>   | Si(CH <sub>3</sub> ) <sub>3</sub> | H                                 | 350                    | 97             | IS         |
| <b>9</b>  | C <sub>7</sub> H <sub>15</sub>  | Si(CH <sub>3</sub> ) <sub>3</sub> | C <sub>3</sub> H <sub>7</sub>     | 340                    | 95             | S          |
| <b>10</b> | C <sub>8</sub> H <sub>17</sub>  | C <sub>2</sub> H <sub>5</sub>     | H                                 | 334                    | 60             | S          |
| <b>11</b> | C <sub>4</sub> H <sub>9</sub>   | F                                 | Si(CH <sub>3</sub> ) <sub>3</sub> | 365                    | 96             | PS         |



**[025]** The tests show that the presence of at least one silyl group (Si(CH<sub>3</sub>)<sub>3</sub>) is essential to obtain UV-A filters with a good stability profile.



**[026]** Example 3:

Preparation of cosmetic compositions

Composition (1): Water-in-oil Emulsion

|                                         |        |
|-----------------------------------------|--------|
| Compound (3)                            | 6 g    |
| PABA (UV-B filter)                      | 2 g    |
| Cetyl dimethicone copolyol (emulsifier) | 7 g    |
| Miglyol 812                             | 40 g   |
| Cetyl alcohol (thickener)               | 1.5 g  |
| Methylparaben (preservative)            | 0.2 g  |
| Distilled water                         | 43.3 g |

The emulsion was prepared by dissolving the compound (3) and PABA in Miglyol 812. The emulsifier, the thickener and the preservative were added. The resulting oil was heated to 80°C, and water was added with rapid stirring.

**[027]** Composition (2): Oil-in-water Emulsion

|                                         |        |
|-----------------------------------------|--------|
| Compound (6)                            | 4 g    |
| Benzophenone (UV-B filter)              | 7 g    |
| Cetyl dimethicone copolyol (emulsifier) | 7 g    |
| Miglyol 812                             | 60 g   |
| Cetyl alcohol (thickener)               | 1 g    |
| Methylparaben (preservative)            | 0.6 g  |
| Distilled water                         | 20.4 g |

The emulsion was prepared by dissolving the compound (6) and benzophenone into Miglyol 812. The emulsifier, the thickener and the preservative were added. The resulting oil was heated to 85°C, and the water was added with rapid stirring.

**[028]** The stability of the compounds of formula (I) in the presence of a UV-B filter was determined in the above compositions.



**[029]** Photostability tests for sunscreens

The compositions were weighed and placed between two plates of quartz. The amount applied was 0.5 mg/cm<sup>2</sup>. The plates were irradiated with a xenon arc solar simulator for 30, 90 and 120 minutes. After the irradiation period, the samples were analysed by comparison of the absorbance spectra before and after exposure. A spectrophotometer was used for determining the absorbance. The area under the curve (AUC) was determined before and after exposure. If the ratio  $AUC_{\text{after}}/AUC_{\text{before}}$  is higher than 0.80, the sunscreen is considered photostable.

**[030]** Table 2

|                 | $AUC_{\text{after}}/AUC_{\text{before}}$ |        |         |
|-----------------|------------------------------------------|--------|---------|
|                 | 30 min                                   | 90 min | 120 min |
| Composition (1) | 0.98                                     | 0.94   | 0.94    |
| Composition (2) | 0.99                                     | 0.95   | 0.93    |

**[031]** As can be seen from table 2, the compositions exhibit good photostability.

**[032]** We provide you with documents D1 and D2. We think they may be relevant to our invention.

**[033]** One of our employees intends to present the results of our research at a conference next week. As far as I understand, this may interfere with the granting of a patent. Please ensure that the application is filed as soon as possible.

**[034]** Please note that it is our company policy not to pay claim fees.



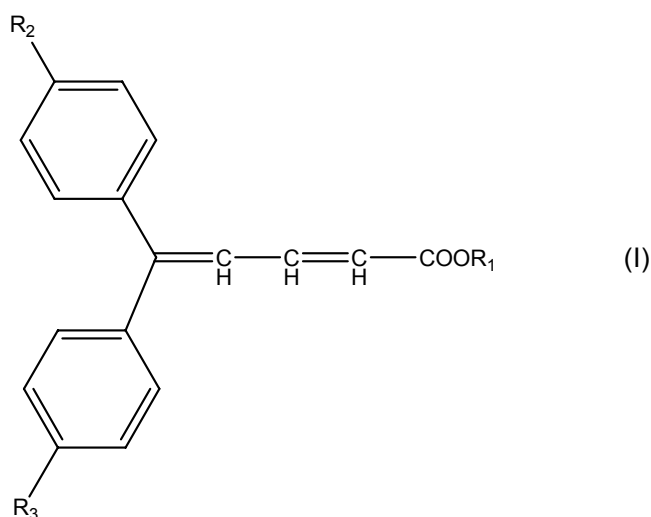
**DOCUMENT D1**

Advances in Polymers, 1969, 270-273

Co-polymerisation reactions of diarylbutadienes

**[001]** Butadiene derivatives are known to react with styrene to provide rubbers with good abrasion resistance and good aging stability. These rubbers are used in particular in car tires. We have now discovered that butadiene derivatives with two aryl groups easily copolymerize with styrene to produce hard rubbers with excellent resistance to high temperatures.

**[002]** The compounds are 4,4-diarylbutadiene derivatives of formula (I) :

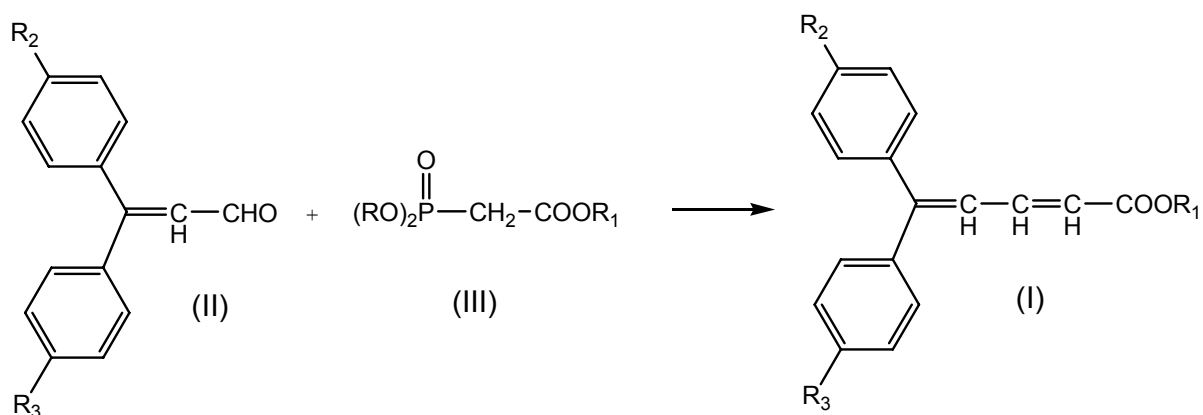


wherein

$R_1$  represents  $C_3$ - $C_{10}$ -cycloalkyl, or phenyl, and

$R_2$  and  $R_3$  independently from each other represent H,  $C_1$ - $C_4$ -alkyl, halogen,  $Si(CH_3)_3$ , OH or  $NH_2$ .

**[003]** The compounds of formula (I) can be prepared by reacting a compound of formula (II) with a compound of formula (III) wherein R is C<sub>1</sub>-C<sub>10</sub>-alkyl, or phenyl. The reaction is carried out in the presence of a base.



**[004]** The process was applied to produce various compounds of formula (I). The monomers obtained are lipophilic and thus remain in the oil phase during the polymerisation reaction.

**[005]** The copolymers were prepared from 180 g of compound of formula (I), 60 g of styrene, 200 ml of Isopar M (oil phase), 1 g of dodecyl mercaptan (stabilizer), 10 g of soap flakes, 340 ml of water, and 20 ml of 3% potassium persulfate solution (initiator). Polymerization was carried out for ten and a half hours. 5 g of phenyl-p-naphthylamine in soap solution were added to the reaction mixture and the polymer was coagulated by adding an aqueous solution of sodium sulfate and sulfuric acid. The polymer was dried in a desiccator. The conversion was 85.5 %.

**[006]** Copolymers with the most promising properties were obtained from a compound of formula (I) wherein R<sub>1</sub> is phenyl, R<sub>2</sub> is methyl and R<sub>3</sub> is Si(CH<sub>3</sub>)<sub>3</sub>. These copolymers exhibit good abrasion resistance and good aging stability together with exceptional properties at high temperatures.

**[007]** Copolymerization of other compounds of formula (I) with styrene also gave rubbery polymers with improved abrasion properties and excellent properties at high temperatures.

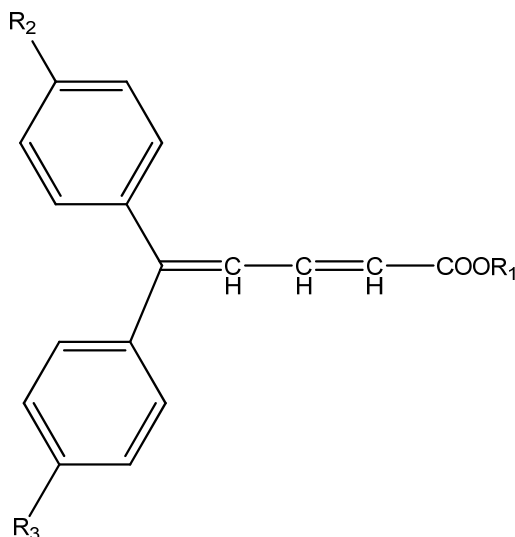


**DOCUMENT D2**

**[001]** The invention deals with new diarylbutadiene derivatives and their use as UV-A filters in cosmetic compositions.

**[002]** In order to absorb most of UV-radiation, modern sunscreens employ a combination of UV-A and UV-B filters. In the last decade, studies have shown that these filters may interact with each other thus leading to a loss of efficiency of the sunscreens. We have found that butadiene derivatives with two aryl substituents are excellent UV-A filters with exceptional properties as regards photostability.

**[003]** The present invention relates to diarylbutadienes of formula (I)



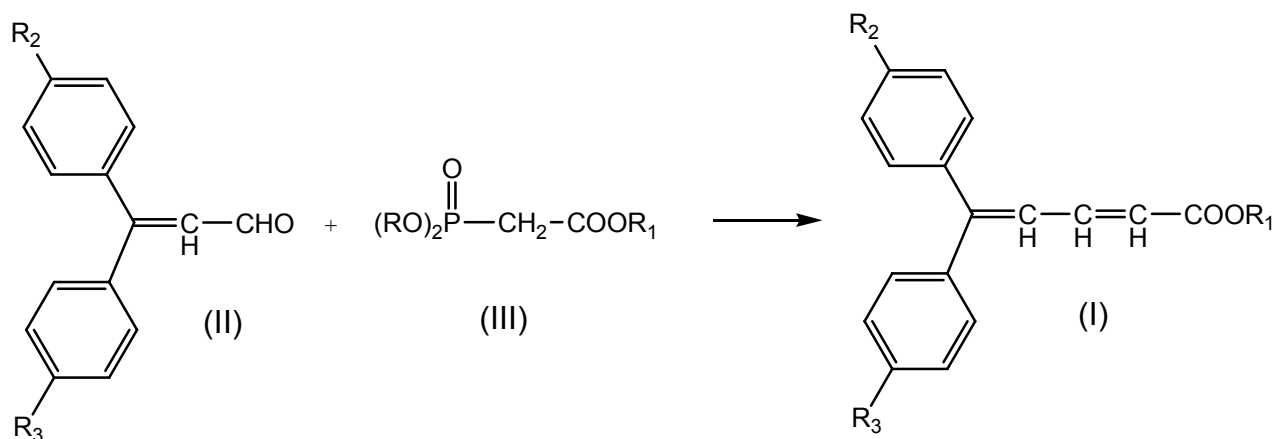
wherein

R<sub>1</sub> represents C<sub>1</sub>-C<sub>4</sub>-alkyl which may be substituted with OH, NH<sub>2</sub> or COOH, and R<sub>2</sub> and R<sub>3</sub> independently from each other represent H, C<sub>1</sub>-C<sub>4</sub>-alkyl, halogen, Si(CH<sub>3</sub>)<sub>3</sub>, OH or NH<sub>2</sub>.

**[004]** Particularly good results are obtained with compounds wherein R<sub>1</sub> is substituted with OH, NH<sub>2</sub> or COOH.



**[005]** The compounds of formula (I) can be prepared by reacting a compound of formula (II) with a compound of formula (III) in the presence of a base as described in *Applied Organic Chemistry*, 1995, pages 1748 - 1750.



wherein R is  $C_1$ - $C_{10}$ -alkyl, or phenyl.

**[006]** The composition according to the invention comprises from 0.1 to 10 wt. %, preferably from 0.2 to 5 wt. %, of the compound of formula (I). The composition also comprises suitable cosmetic carriers. The compositions are typically emulsions. Where oil-in-water or water-in-oil emulsions are used, the presence of an emulsifier is required. Particularly effective emulsifiers are selected from sesquioleates, ethoxylated esters and polysiloxanes (e.g. cetyl dimethicone copolyol).



**[007]** The compositions may also comprise further additives chosen from stabilizers, thickeners, preservatives, moisturizers and perfumes. The total content of additives may vary from 1 to 80 wt. %, preferably from 10 to 30 wt. %, relative to the weight of the composition. Typical examples of stabilizers which can be employed are metal salts of fatty acids such as magnesium stearate, aluminium stearate or zinc stearate. Examples of conventional thickeners are crosslinked polyacrylic acids, polysaccharides, in particular xanthan gum and guar gum, fatty alcohols (e.g. cetyl alcohol), polyacrylates and polyvinylpyrrolidone. Suitable preservatives are chosen from formaldehyde solution, EDTA derivatives or parabens such as methylparaben or propylparaben. The compositions may also comprise other additional UV-A filters and/or UV-B filters chosen from salicylic acid, camphor, benzophenone or p-aminobenzoic acid (PABA).

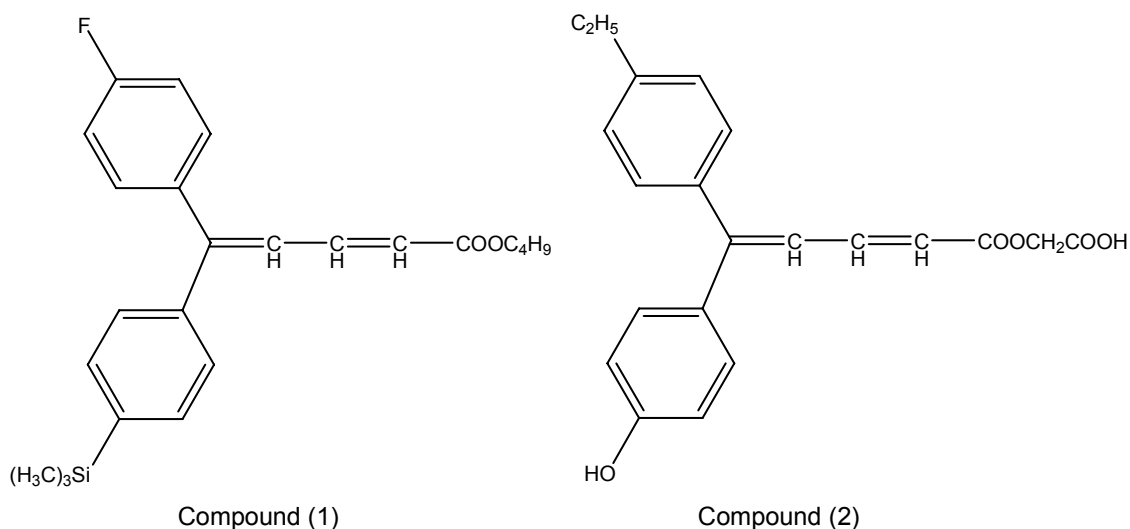
**[008]** The preferred compositions are oil-in-water or water-in-oil emulsions, with oil-in-water emulsions being most preferred. The oil phase consists of esters or triglycerides, in particular, triglycerides of C<sub>8</sub>-C<sub>12</sub> fatty acids.

**[009]** The claimed compounds were prepared according to the process described in *Applied Organic Chemistry*, 1995, pages 1748 - 1750.

**[010]** The compounds were tested for their photostability. Their absorbance was also determined. The compounds according to the invention absorb in the UV-A range and exhibit a photostability of 80% or higher.



**[011]** In particular, compounds (1) and (2) show excellent stability profiles with a photostability of 94% and 97% respectively.



**[012]** The compositions can be produced by known methods. The following compositions were prepared:

**[013]** Composition (1): Oil-in-Water Emulsion

|                                         |        |
|-----------------------------------------|--------|
| Compound (1)                            | 1 g    |
| PABA (UV-B filter)                      | 2 g    |
| Cetyl dimethicone copolyol (emulsifier) | 2 g    |
| Miglyol 812 (oil phase)                 | 12 g   |
| Cetyl alcohol (thickener)               | 1.7 g  |
| Methylparaben (preservative)            | 0.2 g  |
| Distilled water                         | 81.1 g |

The emulsion was prepared by dissolving the compound (1) and PABA into Miglyol 812. The emulsifier, the thickener and the preservative were added. The resulting oil was heated to 80°C, and water was added with rapid stirring.



**[014]** Composition (2): Oil-in-water Emulsion

|                                         |        |
|-----------------------------------------|--------|
| Compound (2)                            | 2 g    |
| Benzophenone (UV-B filter)              | 4 g    |
| Cetyl dimethicone copolyol (emulsifier) | 4 g    |
| Miglyol 812 (oil phase)                 | 10 g   |
| Cetyl alcohol (thickener)               | 1 g    |
| Methylparaben (preservative)            | 0.6 g  |
| Distilled water                         | 78.4 g |

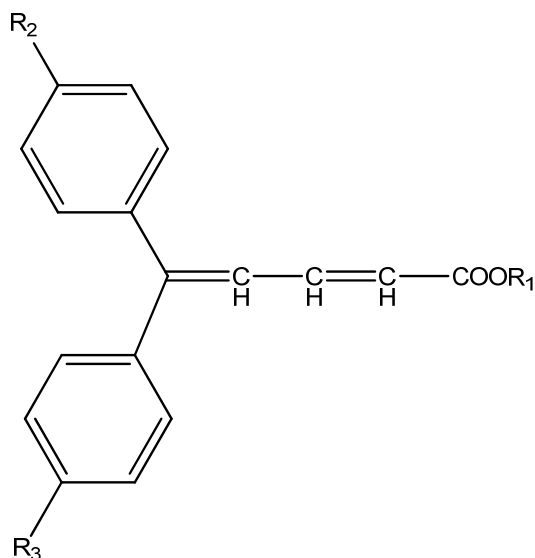
The emulsion was prepared by dissolving the compound (2) and benzophenone in Miglyol 812. The emulsifier, the thickener and the preservative were added. The resulting oil was heated to 80°C, and water was added with rapid stirring.

**[015]** The new compounds can be used in products formulated to feel lighter and less oily, such as daily-use cosmetic moisturizers.



# Claims

1. Compounds of formula (I)



wherein

R<sub>1</sub> represents C<sub>1</sub>-C<sub>4</sub>-alkyl which may be substituted with OH, NH<sub>2</sub> or COOH, and R<sub>2</sub> and R<sub>3</sub> independently from each other represent H, C<sub>1</sub>-C<sub>4</sub>-alkyl, halogen, Si(CH<sub>3</sub>)<sub>3</sub>, OH or NH<sub>2</sub>.

2. Cosmetic compositions comprising at least one compound according to claim 1, an emulsifier, a stabilizer, a thickener and a preservative.

