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Substituted benzylidenecyanoacetic acid esters

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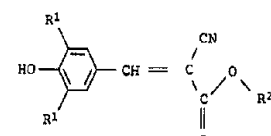
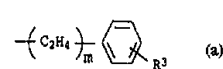
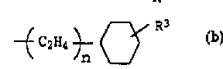
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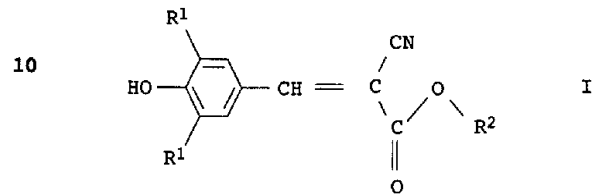
<p>(51) Internationale Patentklassifikation ⁶ ; A61K 7/42, G03C 1/815</p>	<p>A1</p>	<p>(11) Internationale Veröffentlichungsnummer: WO 97/15279 (43) Internationales Veröffentlichungsdatum: 1. Mai 1997 (01.05.97)</p>
<p>(21) Internationales Aktenzeichen: PCT/EP96/04417 (22) Internationales Anmeldedatum: 11. Oktober 1996 (11.10.96) (30) Prioritätsdaten: 195 39 189.6 20. Oktober 1995 (20.10.95) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): BASF AKTIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): TRENTMANN, Beate [DE/DE]; Kranichweg 5, D-68307 Mannheim (DE). (74) Gemeinsamer Vertreter: BASF AKTIENGESELLSCHAFT; D-67056 Ludwigshafen (DE).</p>	<p>(81) Bestimmungsstaaten: AU, CA, CN, JP, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</p>	
<p>(54) Title: SUBSTITUTED BENZYLIDENECYANOACETIC ACID ESTERS</p>		
<p>(54) Bezeichnung: SUBSTITUIERTE BENZYLIDENCYANESSIGESTER</p>		
<div style="text-align: center;">  <p style="text-align: right;">(I)</p> </div> <div style="text-align: center; margin-top: 20px;">  <p>(a)</p> </div> <div style="text-align: center; margin-top: 10px;">  <p>(b)</p> </div>		
<p>(57) Abstract</p>		
<p>The invention concerns compounds of the formula (I) in which R¹ = iso-propyl, iso-butyl or t-butyl and R² = alkyl with 6-14 C-atoms, (a), (b), R³ being H or C₁-C₄ alkyl and m and n being 0 or 1.</p>		
<p>(57) Zusammenfassung</p>		
<p>Verbindung der Formel (I), worin R¹ = i-Propyl, i-Butyl oder t-Butyl, R² = Alkyl mit 6-14 C-Atomen, (a), (b), mit R³ = H oder C₁-C₄-Alkyl und m, n = 0 oder 1 bedeuten.</p>		

Substituted benzylidenecyanoacetic esters

Abstract

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A compound of the formula I



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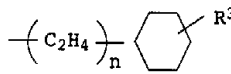
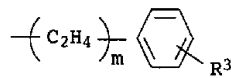
where

R¹ is i-propyl, i-butyl or t-butyl,

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R² is alkyl with 6-14 carbon atoms,

25



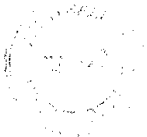
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with R³ = H or C₁-C₄-alkyl
and m, n = 0 or 1.

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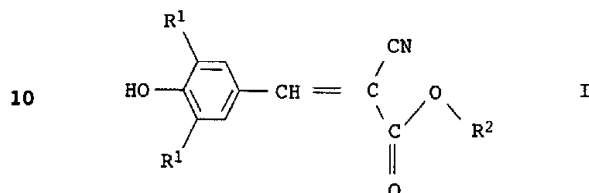
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Substituted benzylidenecyanoacetic esters

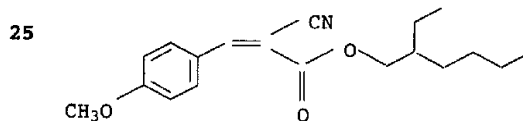
The present invention relates to substituted
5 benzylidenecyanoacetic esters of the formula I



15 to the use thereof as sunscreen agents, to the use thereof in
cosmetic products, and to cosmetic compositions comprising these
compounds.

Sunscreen agents based on substituted benzylidenecyanoacetic
20 esters are known.

BE 757 036 describes, inter alia, the compound



30 as light-sensitive photomaterial.

DE 10 87 902 describes condensates of benzaldehydes with
compounds containing active methylene groups. Among many other
compounds, mention is also made of condensates of

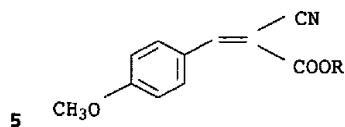
35 4-hydroxy-3,5-di-*t*-butylbenzaldehyde with diethyl malonate,
cyanoacetic ester, malononitrile or malonic acid (page 1, second
column, group VI). These compounds are described as suitable
light stabilizers for films, sheets, fibers and filaments.

40 DE 28 16 819 describes substituted benzylidenecyanoacetic esters
of the following structure as UV-A filters:

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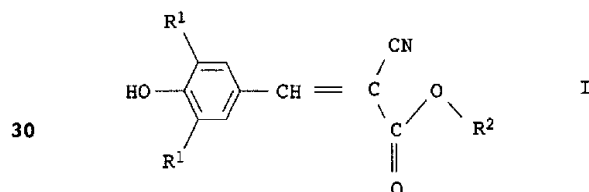
it being found that, with regard to possible substitution on the aromatic ring, para monosubstitution represents the optimum and, in turn, the methoxy radical confers optimal properties here.

10 Concerning the radical R, it is found that compounds with R = n-hexyl, n-octyl, n-decyl, isononyl, and isodecyl are most suitable.

Since cosmetic sunscreen agents must, besides the photoproperties
 15 such as suitable absorption maximum, high specific extinction and photostability, have a number of other use properties such as good oil solubility, pH stability, oxidation stability, thermal stability, minimum intrinsic color and no intrinsic odor and, moreover, must also be toxicologically acceptable, it is an
 20 object of the present invention to optimize the previously disclosed products in respect of the abovementioned properties.

We have found that this object is achieved in that compounds of the formula I

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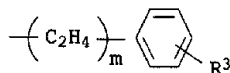
where

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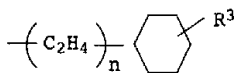
R¹ is i-propyl, i-butyl or t-butyl,

R² is alkyl with 6-14 carbon atoms,

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with R³ = H or C₁-C₄-alkyl

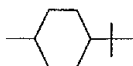


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and m, n = 0 or 1,

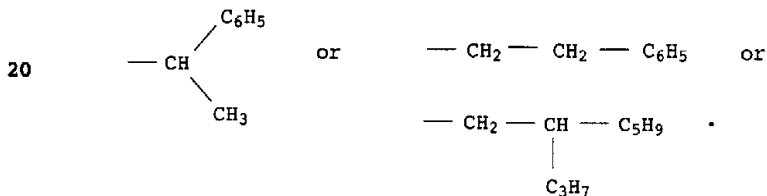
have better properties in respect of many of the abovementioned requirements, especially in respect of the photostability, than 5 prior art compounds.

Particularly suitable sunscreen agents have been found to be compounds of the formula I where both R¹ radicals are tert-butyl and R² is a branched alkyl radical with 8-12 carbon atoms or 10 -C₂H₄-C₆H₅ or



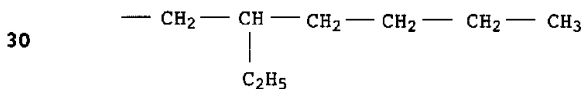
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Moreover R² can be, for example, the radical



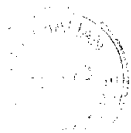
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A particularly advantageous compound of the formula I is the one in which both R¹ radicals are tert-butyl and R² is



The compounds according to the invention can be prepared in a 35 conventional way from the corresponding benzaldehydes and cyanoacetic esters in a Knoevenagel condensation (see, for example, Organikum, 1988 edition, page 459). The corresponding cyanoacetic esters were prepared by transesterification of a commercially obtainable cyanoacetic ester with the appropriate 40 alcohol in a conventional way.

The compounds according to the invention are particularly suitable as light stabilizers for materials which are attacked by UV rays, for example filaments, fibers, sheets, films and other 45 plastic moldings.



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The compounds according to the invention are particularly suitable for protecting the human skin from UV rays. They can be used in a wide variety of cosmetic and medicinal products such as sun oils, sun creams, sun lotions, sun gels, lipsticks, skin
5 creams, hair gels and non-greasy gels.

Examples

Example 1

10

2-Phenylethyl

3,5-di-tertiary-butyl-4-hydroxybenzylidenecyanoacetate

5.9 g of 3,5 di-tertiary-butyl-4-hydroxybenzaldehyde are [sic]
15 dissolved in 50 ml of toluene.

4.7 g of 2-phenylethyl cyanoacetate, 0.1 g of piperidine and
0.25 g of acetic acid were heated to reflux. 0.4 g of H₂O was
removed azeotropically in 2 h. The mixture was cooled, washed
20 with water and with sodium bicarbonate solution, dried and
concentrated. The crude product was recrystallized.
Yield: 9.9 g (98%).

Example 2

25

2-Ethylhexyl 3,5-di-tertiary-butyl-4-hydroxybenzylidene-
cyanoacetate

28.1 g of 3,5-di-tertiary-butyl-4-hydroxybenzaldehyde were
30 dissolved in 60 ml of toluene. 21.7 g of 2-ethylhexyl
cyanoacetate, 0.27 g of piperidine and 0.67 g of acetic acid were
added. The mixture was heated to reflux, and about 2 g of water
were removed azeotropically. The clear solution was washed, dried
and concentrated.
35 Yield: 46.2 g of pale yellow oil (93%).

Example 3

4-Tertiary-butylcyclohexyl 3,5-di-tertiary-butyl-4-hydroxy-
40 benzylidenecyanoacetate

5.4 g of 3,5-di-tertiary-butyl-4-hydroxybenzaldehyde were
dissolved in 50 ml of toluene. 5.9 g of
4-tertiary-butylcyclohexyl cyanoacetate, 0.1 g of piperidine and
45 0.25 g of acetic acid were added. 0.4 g of water was removed
azeotropically under reflux. The mixture was washed, dried and



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concentrated.

Yield: 10.6 g (96%) of crystals

Properties:

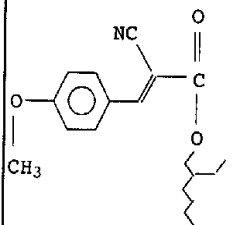
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Example	λ_{\max} [nm]	E_1^A	Solubility	Photostability
1	356	484	good	98%
2	357	638	very good	99%
3	355	623	good	92%

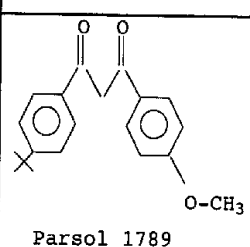
The solubility was determined by dissolving the substances in C_{12} - C_{15} -alkyl benzoates at room temperature.

15 The photostability was determined by irradiating a solution of the appropriate compound with a Heräus Sun-Test apparatus for 30 min. The amount of the compound still present is indicated as a percentage of the initial amount.

20 Comparative Example 1

	λ_{\max} [nm]	E_1^A	Solubility	Photostability
<p>25</p>  <p>30</p>	342	904	very good	79%

Comparative Example 2

	λ_{\max} [nm]	E_1^A	Solubility	Photostability
<p>35</p>  <p>40</p> <p>Parsol 1789</p>	357	638	good	55%

Parsol 1789 is a licenced commercial product (UV-A filter).

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It is evident that the compounds according to the invention display surprising advantages, especially in the important property of photostability, compared with a known compound of similar structure and compared with a licenced commercial product.

Use Examples

10 Cosmetic compositions in which the compounds according to the invention can be used with particular advantage are indicated below.

15 General method for producing emulsions for cosmetic purposes:

All the oil-soluble ingredients are heated to 85°C in a stirred vessel.

20 When all the ingredients have melted and are in the form of a liquid phase, the aqueous phase is incorporated with homogenization.

25 While stirring, the emulsion is cooled to about 40°C, perfume is added, and the mixture is then homogenized and cooled to 25°C while stirring continuously.

Composition for the lip salve

30 ad 100 Eucerinum anhydricum
10.00 Glycerol
10.00 Titanium dioxide
0.5-10 Compound from Example 1
35 8.00 Octyl methoxycinnamate
5.00 Zinc oxide
4.00 Castor oil
4.00 Pentaerythrithyl [sic] stearate/caprate/caprylate
adipate [sic]
40 3.00 Glyceryl stearate SE
2.00 Beeswax
2.00 Microcrystalline wax
2.00 Quaternium-18 bentonite
1.50 PEG-45/Dodecyl glycol copolymer

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Composition for sunblocker with micropigments

	ad 100	Water
	10.00	Parsol MCX octyl methoxycinnamate [sic]
5	6.00	PEG-7-hydrogenated castor oil
	6.00	Titanium dioxide
	0.5-10	Compound from Example 1
	5.00	Mineral oil
	5.00	Isoamyl p-methoxycinnamate
10	5.00	Propylene glycol
	3.00	Jojoba oil
	3.00	4-Methylbenzylidene camphor
	2.00	PEG-45/dodecyl glycol copolymer
	1.00	Butyl methoxydibenzoylmethane
15	1.00	Dimethicone
	0.50	PEG-40-hydrogenated castor oil
	0.50	Tocopheryl acetate
	0.50	Phenoxyethanol
	0.20	EDTA
20		Non-greasy gel
	ad 100	Water
	8.00	Octyl methoxycinnamate
25	7.00	Titanium dioxide
	0.5-10	Compound of Example 2
	5.00	Glycerol
	5.00	PEG-25 PABA
	1.00	4-Methylbenzylidene camphor
30	0.40	Acrylates C10-C30 alkyl acrylate crosspolymer [sic]
	0.30	Imidazolidinyl urea
	0.25	Hydroxyethyl cellulose
	0.25	Sodium methylparaben
	0.20	Disodium EDTA
35	0.15	Fragrance
	0.15	Sodium propylparaben
	0.10	Sodium hydroxide

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Sun cream (SPF 20)

	ad 100	Water
	8.00	Octyl methoxycinnamate
5	8.00	Titanium dioxide
	6.00	PEG-7-hydrogenated castor oil
	0.5-10	Compound of Example 2
	6.00	Mineral oil
	5.00	Zinc oxide
10	5.00	Isopropyl palmitate
	5.00	Imidazolidinyl urea
	3.00	Jojoba oil
	2.00	PEG-45/dodecyl glycol copolymer
	1.00	4-Methylbenzylidene camphor
15	0.60	Magnesium stearate
	0.50	Tocopheryl acetate
	0.25	Methylparaben
	0.20	Disodium EDTA
	0.15	Propylparaben

20

Sun cream, water-resistant

	ad 100	Water
	8.00	Octyl methoxycinnamate
25	5.00	PEG-7-hydrogenated castor oil
	5.00	Propylene glycol
	4.00	Isopropyl palmitate
	4.00	Caprylic/capric triglyceride
	0.5-10	Compound of Example 2
30	4.00	Glycerol
	3.00	Jojoba oil
	2.00	4-Methylbenzylidene camphor
	2.00	Titanium dioxide
	1.50	PEG-45/dodecyl glycol copolymer
35	1.50	Dimethicone
	0.70	Magnesium sulfate
	0.50	Magnesium stearate
	0.15	Fragrance

40 Sun lotion (SPF 6)

	ad 100	Water
	10.00	Mineral oil
	6.00	PEG-7-hydrogenated castor oil
45	5.00	Isopropyl palmitate
	3.50	Octyl methoxycinnamate
	0.5-10	Compound of Example 2

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3.00	Caprylic/capric triglyceride
3.00	Jojoba oil
2.00	PEG-45/dodecyl glycol copolymer
0.70	Magnesium sulfate
5 0.60	Magnesium stearate
0.50	Tocopheryl acetate
0.30	Glycerol
0.25	Methylparaben
0.15	Propylparaben
10 0.05	Tocopherol

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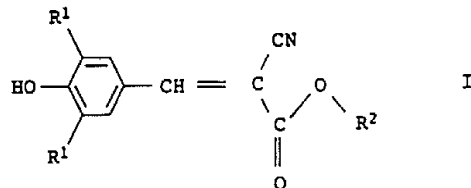
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

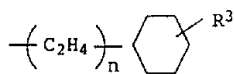
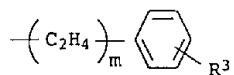
1. A compound of the formula I



where

R¹ is i-propyl, i-butyl or t-butyl,

R² is alkyl with 6-14 carbon atoms,

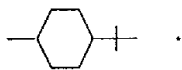


with R³ = H or C₁-C₄-alkyl
and m, n = 0 or 1.

2. A compound of the formula I as claimed in claim 1, where

R¹ is t-butyl and

R² is a branched alkyl radical with 8-12 carbon atoms,
-C₂H₄-C₆H₅ or

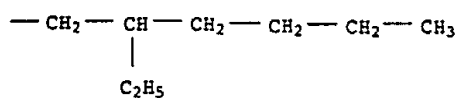


3. A compound of the formula I as claimed in claim 1, where

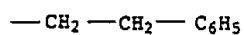
R¹ is t-butyl and

R² is





or



4. The use of a compound as claimed in claim 1 as sunscreen agent or light stabilizer.
5. The use of a compound as claimed in claim 1 in cosmetic products.
6. A cosmetic composition which includes as sunscreen agent a compound as claimed in claim 1 alone or together with other UV-A or UV-B filters.
7. A compound of formula I according to claim 1 and as herein described with reference to examples 1 to 3.
8. The use of a compound according to claim 5 and as herein described with reference to the use examples.

DATED this 14th day of October 1999

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