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653010

NOTICE OF ENTITLEMENT

I, John Gordon Hinde, Patent Attorney

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being authorised by the Applicant(s)/Nominated Person(s) in respect of an application entitled:

Light Screening Agent

state the following:-

1. The Applicant(s)/Nominated Person(s) has/have, for the following reasons, gained entitlement from the actual inventor(s):-

The Applicant/Nominated Person is the assignee of L. Givaudan & Cie
Societe Anonyme which is the assignee of the inventor.

- 2a.* ~~The Applicant(s)/Nominated Person(s) is/are the applicant(s) of the of the basic application(s) listed* on the Patent-Request/* in the Declaration under Article 8 of the PCT.~~

- 2b.* The Applicant(s)/Nominated Person(s) is/are entitled to rely on the basic application(s) listed* on the Patent-Request/* in the Declaration under Article 8 of the PCT as follows:
L. Givaudan & Cie Societe Anonyme made the basic applications as assignee of the inventors, and have assigned their interest in the priority rights accruing from the basic applications to the Applicant/Nominated Person.

- 3.* The basic application(s) listed *on the Patent Request/* in the Declaration under Article 8 of the PCT is/are the application(s) first made in a Convention Country in respect of the invention.

- 4a.* ~~The Applicant(s)/Nominated Person(s) is/are the depositor(s) of the deposit(s) listed in the Schedule hereto.~~

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DATED this FIRST

day of FEBRUARY

19 93

(Signature)

John Gordon Hinde, Patent Attorney

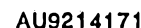
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* Delete if not applicable.

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LIGHT SCREENING AGENT

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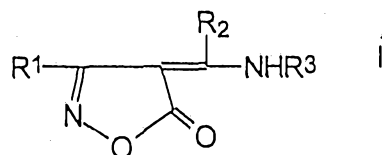
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(57) The compounds of formula I are particularly suitable as light screening agents. The invention is accordingly also concerned with the use of I as light screening agents.

Claim

1. A light screening composition which contains a compound of the formula



wherein

R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower alkyl or oxy-lower alkyl substituted phenyl,

R² represents H, C₁₋₂₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,

R³ represents H, C₁₋₁₉-alkyl, C₁₋₁₉-hydroxyalkyl, C₁₋₁₉-polyhydroxyalkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl, or optionally lower alkyl or oxy-lower alkyl substituted pyridyl, a polyether residue, a phenylsulphonic acid residue

and

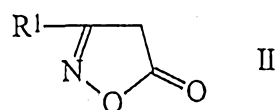
R² and R³ together with the N atom can also form a ring; together with an acceptable carrier, diluent, excipient and/or adjuvant.

(11) AU-B-14171/92

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(10) 653010

10. A process for the manufacture of the compounds of formula I' in accordance with claim 6, which process comprises appropriately substituting an isoxazolone



wherein R¹ has the above significance, in the 4-position.

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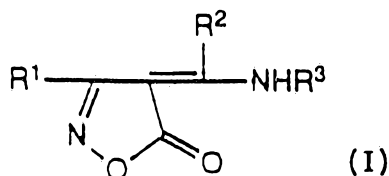
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(54) Title: LIGHT SCREENING AGENT

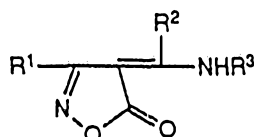


(57) Abstract

Light screening compositions which contain a compound of formula (I), wherein R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl, R² represents H, C₁₋₂₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl, R³ represents H, C₁₋₁₉-alkyl, C₁₋₁₉-hydroxyalkyl, C₁₋₁₉-polyhydroxyalkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl or optionally lower-alkyl or oxy-lower alkyl substituted pyridyl, a polyether residue, a phenylsulphonic acid residue and R² and R³ together with the N atom can also form a ring.

Light Screening Agent

The invention is concerned with light screening compositions which contain isoxazolones, namely compounds of the
 5 formula



wherein

- 10 R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,
 R² represents H, C₁₋₂₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted
 15 phenyl,
 R³ represents H, C₁₋₂₉-alkyl, C₁₋₁₉-hydroxyalkyl, C₁₋₁₉-polyhydroxyalkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl or optionally lower-alkyl or oxy-lower alkyl
 20 substituted pyridyl, a polyether residue, a phenylsulphonic acid residue,

and

R² and R³ together with the N atom can also form a ring.

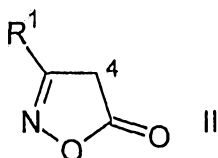
25 The compounds of formula I are particularly suitable as light screening agents. The invention is accordingly also concerned with the use of I as light screening agents.

The compound of formula I are partly novel and partly
 30 known.

The novel compound I, namely the compounds I', correspond to those compounds of formula I above in which the sum of the carbon atoms of R¹ + R² + R³ = 9-30 and the number of
 35 phenyl residues per molecule does not exceed 1.

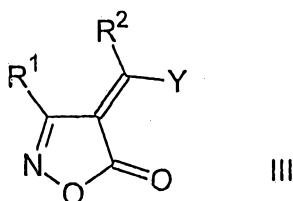
These novel compounds I and the process for their manufacture form further objects of the present invention.

The process comprises appropriately substituting an isoxazolone of the formula



5 wherein R¹ has the above significance, in the 4-position

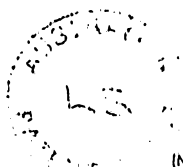
This substitution of II is conveniently effected by reacting II with a R²-substituted carboxylic acid derivative of the formula A, B, C or D as given below. There is thus formed first of all a compound of the formula



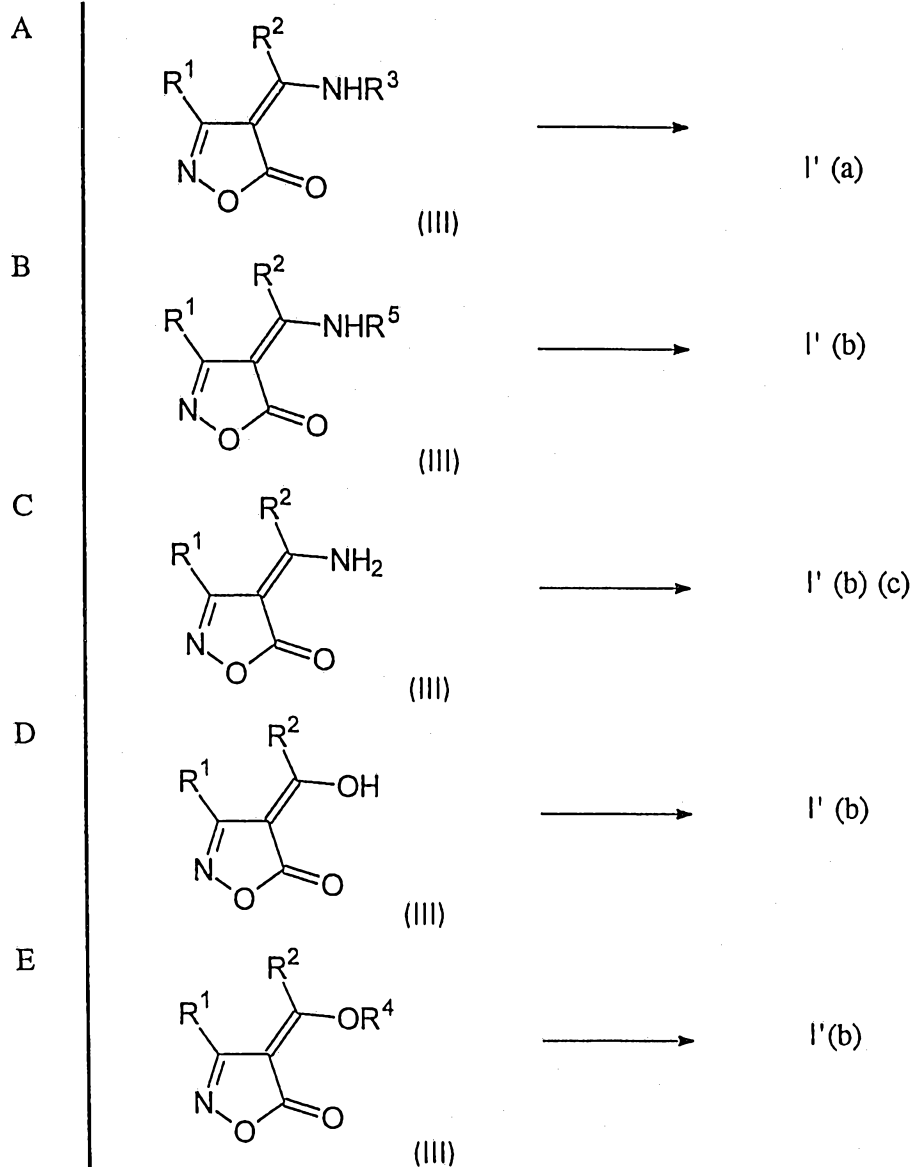
10 Y signifies NHR³, OH, O-lower alkyl, halogen, NH₂, NH⁵-see page 3.

Examples of the aforementioned carboxylic acid derivatives used as reagents are

- | | | |
|------|---------------------|---|
| A | $R^2-C(=NR^3)(-X)$ | wherein X is a leaving group = -halogen,
- OR⁴ (in which R⁴ = lower alkyl),
-NHR³ |
| 15 B | $R^2-C(=NR^5)(-X)$ | R⁵ = H,
lower alkyl;
≠ R³ |
| C | $R^2-C(=NH_2+)(-X)$ | |
| D | $R-C(=O)(-X)$ | |
| 20 E | $R^2-C(OR^4)_3$ | |



There are thereby formed the products III reagents



(a) Where $Y = \text{NHR}^3$ in formula III the desired end product I' therefore results directly.

(b) If however, $Y \neq \text{NHR}^3$ then the grouping $Y = \text{NHR}^3$ is conveniently introduced in a subsequent, secondary reaction step and the compound I' is thus obtained. This is carried out e.g. by reacting any compound III with an amine R^3NH_2 .

(c) In case C, R^3 can also be introduced by reaction of (III) with a halide R^3Hal (F, Cl, Br, I) or a corresponding epoxide such as e.g. $(\text{CH}_2)_2\text{O}$, etc.

The secondary reaction step ($\text{III} \rightarrow \text{I}'$) can be effected, e.g. in E simultaneously with the primary reaction.



Depending on the structure of the amine $R^3N H_2$ or its residue R^3 , which can carry more than one amino substituent molecules with several, e.g. 2 or 3, isoxazole residues can also be formed. One such amine would be e.g. a polyoxypropylenediamine, e.g. of the formula $NH_2CH[CH_3]CH_2(OCH_2CH_2[CH_3])_nNH_2$, or a polyoxy - ethylenediamine, 5 e.g. of the formula $NH_2CH_2CH_2(OCH_2CH_2)_nNH_2$, in which n signifies e.g. a whole number of 1 to 30.

The reactions are conveniently carried out using methods per se.

A or the primary step of B-E is conveniently carried out in a temperature range of about 0-150°C. It is carried out, if desired, in the presence of an inert solvent, e.g. diethyl 10 ether, tetrahydrofuran, dioxan, toluene, xylene, dichloromethane, dichloroethane, etc.

If desired, the reaction is carried out in the presence of a base, preferably a weak base such as e.g. a tertiary amine, e.g. triethylamine, dimethylaniline, dimethylaminopyridine or diazabicyclooctane, or an inorganic base such as e.g. sodium phosphate, soda, potash, magnesium hydroxide or oxide; although sodium hydroxide or potassium hydroxide also 15 comes into consideration. The reaction is conveniently carried out in a temperature range of 0-200°C, especially of 20-150°C.

In the case of the secondary step of B to E, the addition of the primary amine R^3NH_2 is conveniently effected in a temperature range of about 0-200°C, especially of 50-160°C, optionally under pressure. The use of a solvent is optional. The aforementioned solvents 20 come into consideration.

In case of the halide R^3Hal , the addition of this halide is optionally effected in the presence of a base, preferably a strong base e.g. an alcoholate, an amide, an alkali hydroxide, etc. The



convenient temperature range is that given above. The addition of a solvent is optional.

In the case of the epoxide, its addition is conveniently
5 effected in the presence of a catalyst, e.g. a strong base or a strong acid. Examples are: alkali hydroxides, alcoholates, mineral acids, Lewis acids, etc. The convenient reaction conditions are as given above.

10 The purification of the resulting compound I can be effected, for example, by crystallization or distillation.

The above reactions are in principle reactions with activated
15 carboxylic acid derivatives, which are reacted with isoxazolones II which are unsubstituted in the 4-position.

The starting materials are known or can be prepared according to methods known per se. Thus, e.g., activated
20 carboxylic acid derivatives are described in Houben-Weyl, Methoden der organischen Chemie [Volume E5 (1985)] by J. Falbe, and [Volume E4 (1983)] by H. Haggmann.

Suitable C₁₋₂₉-alkyl residues are, for example:

25 C₁₋₁₂-alkyl residues, but also higher, e.g. C₁₅-, C₁₈-, C₂₀-, C₂₁-, C₂₄-, C₂₇-, C₂₉- residues, and also lower alkyl (C₁₋₆) residues, e.g. methyl, ethyl, propyl, butyl, hexyl, etc.

Suitable C₂₋₂₉-alkenyl residues are, for example:

30

C₂₋₁₂- α -alkenyl, C₂₋₁₂- ω -alkenyl, C₂₋₆-alkenyl, especially allyl, methallyl, Δ^2 -butenyl, Δ^3 -butenyl, ω -hexenyl, etc.

Suitable C₂₋₂₉-alkynyl residues are in particular C₂₋₆-alkynyl
35 residues, e.g. 2-propynyl, 3-butynyl, 4-pentynyl, 1,1-dimethylpropynyl, ω -hexynyl, etc.

Examples of lower-alkyl and, respectively, the lower-alkyl part of oxy-lower alkyl are: OCH_3 , OC_2H_5 , OC_5H_{11} , OC_6H_{13} , etc.

Examples of C_{1-29} -hydroxyalkyl residues are $\text{CH}_2\text{CH}_2\text{OH}$,
 5 $\text{CH}_2\text{CH}_2(\text{CH}_3)\text{OH}$, $\text{CH}(\text{OH})(\text{CH}_2)_n\text{H}$ with $n = 2-28$, or as illustrated e.g. in Example 16.

Examples of C_{1-29} -polyhydroxyalkyl residues are
 $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{CH}_2(\text{CHOH})_n\text{CH}_2\text{OH}$, $(\text{CHOH})_n\text{-CH}_2\text{OH}$,
 10 $\overline{\text{CH}(\text{CHOH})_n\text{CH}_2\text{OCHOH}}$, $\overline{\text{CH}(\text{CHOH})_n\text{CH}(\text{CH}_2\text{OH})\text{OCHOH}}$ with $n = 1-28$, especially 1-4.

Examples of polyether residues are polyethylene glycol residues, polypropylene glycol residues, e.g. $(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$ or
 15 $[\text{CH}(\text{CH}_3)\text{CH}_2\text{O}]_n\text{H}$ with $n = 2-20$, as illustrated e.g. in Examples 18 and 19.

All the residues R^1 , R^2 and R^3 can be straight-chain or
 20 branched.

R^2 and R^3 together with the N atom can also form a - saturated or unsaturated- ring, e.g. a 5- or 6-membered ring such as e.g. the pyrrolidinyl ring.

25 The total number of carbon atoms of R^1 and R^2 and R^3 conveniently does not exceed 30; because otherwise the relationship of the sizes of the residues R^1 , R^2 and R^3 compared with the light-absorbing part of the molecule (chromophore, i.e. the isoxazolone part) is unfavourable.

30

The preferred residues in the case of the different substituents are as follows:

- 1) R^1 = methyl, but also hexyl and phenyl,
 35 R^2 = H or C_{3-11} -alkyl,
 R^3 = C_{3-20} -alkyl, substituted phenyl;

- 2) as 1) whereby R^2 and R^3 together have 5-15, especially 9-13, C atoms;
- 3) as 1), whereby $R^2 = H$ and $R^3 = C_{8-16}$ -alkyl, especially C_{10-12} -alkyl;
- 4) $R^1 =$ methyl, but also hexyl and phenyl, R^2 or $R^3 =$ phenyl, pyridyl, optionally substituted, and the other residue (R^3 or R^2) = C_{5-20} -alkyl, especially C_{7-14} - or C_{9-12} -alkyl.

Essential requirements of (especially cosmetic) UV filters are e.g.:

- high extinction (1) (and associated therewith low dosing and therefore reduced toxicological risk);
- high stability against the influence of light (2);
- stability against acids, bases, air and other chemical or thermal influences (3);
- good oil solubility (4) and/or good water solubility;
- low tendency to crystallize-out, e.g. from emulsions even at low temperatures (e.g. in snow);
- toxicological safety;
- lack of colour and lack of smell (5);
- favourable price, inexpensive to use (6);
- water resistance (substantivity);
- very good compatibility with other cosmetic ingredients and simplicity in handling (7).

The compounds I' are very well suited as light screening agents because they generally fulfil a majority of the foregoing requirements, especially parameters (1), (2), (3), (4), (5), (6) and (7) set forth above.

5

It is quite generally true that the UV filters of structure I are novel chromophores having a high photostability.

The compounds of Examples 1, 2, 3, 4, 10, 11, 12, 14, 15, 16, 10 18, 20 and 21 hereinafter are especially preferred because they fulfil these requirements in a particular manner.

The manufacture of the novel light screening compositions (especially of skin protection and, respectively, sunscreen 15 preparations for everyday cosmetics) comprises incorporating a compound of general formula I into a cosmetic base which is suitable for light screening compositions. Where convenient, other conventional UV A or UV B filters can also be combined during this incorporation.

20

Such UV A filters are, for example:

1-(4-methoxyphenyl)-3-(4-tert.-
butylphenyl)propane-1,3-dione

25 CTFA name: butylmethoxydibenzoylmethane

4-Isopropyl-dibenzoylmethane

2,2'-Hydroxy-4-methoxybenzophenone (= 30 dioxibenzene or benzophenone- δ)

2-Hydroxy-4-methoxybenzophenone-5-sulphonic
acid (= sulisobenzene, benzophenone-4)

35 2-Hydroxy-4-methoxybenzophenone (= oxybenzene,
benzophenone-3)

3,3,5-Trimethyl-cyclohexyl-N-acetyl-anthranilate
(= homomenthyl N-acetyl-anthranilate)

2-Methylanthranilate

5

Usual UV B filters such as, for example, the following organic compounds belonging to the widest classes of substances can be mentioned as UV B filters i.e. as substances having absorption
10 maxima between about 290 and 320 nm:

- 1) p-Aminobenzoic acid derivatives, such as e.g. ethyl p-aminobenzoate and other esters, such as propyl, butyl, isobutyl p-aminobenzoate, ethyl p-dimethylaminobenzoate, glyceryl p-aminobenzoate, amyl p-dimethylaminobenzoate.
15
- 2) Cinnamic acid derivatives such as e.g. 2-ethoxyethyl p-methoxycinnamate, 2-ethylhexyl p-methoxycinnamate, p-methoxycinnamic acid ester mixtures, cinnamic acid ester
20 mixtures.
- 3) Dibenzalazine.
- 4) Heterocyclic nitrogen compounds such as 2-phenylbenzimidazole derivatives, e.g. 2-phenylbenzimidazole-5-sulphonic acid.
25
- 5) Salicylic acid derivatives such as e.g. menthyl salicylate, homomenthyl salicylate, phenyl salicylate.
30
- 6) Benzophenone derivatives such as e.g. 4-phenylbenzophenone, 4-phenylbenzophenone-2-carboxylic acid isooctyl ester, 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid.
- 35 7) Coumarin derivatives such as e.g. 7-oxycoumarin, β -umbelliferoneacetic acid, 6,7-dioxycoumarin.
- 8) Gallic acid derivatives such as e.g. digalloyl trioleate.

- 9) Arylidenecycloalkanones such as e.g. benzylidenecamphor.
- 10) Anthranilic acid derivatives such as e.g. menthyl
5 anthranilate.
- 11) Hydroxyphenylbentriazole.

As usual cosmetic bases for the light screening compositions
10 in the scope of the present invention there can be used any usual
preparation which corresponds to the cosmetic requirements, e.g.
creams, lotions, emulsions, salves, gels, solutions, sprays, sticks,
milks and the like. The light screening effect will, of course, also
be dependent on the base which is used. The intensity of the light
15 screening activity also depends in the case of the same base on
the concentration of active ingredient. Suitable concentrations are
e.g. between 1-6%, preferably between 2-5%, of a compound of
formula I in the cosmetic preparation.

20 The light screening agents are, however, also suitable
against the damaging influence of light on other substrates to be
protected. As such further substrates there come into
consideration e.g.: plastics and synthetic resins, soft resins, e.g. for
contact lenses, varnishes, oils, waxes, furniture and car polishes,
25 etc.

Example 1

4-[1-(N-Pentylamino)-1-hexylidene]-3-methylisoxazol-5(4H)-one

30

a) N-Pentyl-caproamide:

275 g of caproyl chloride are added dropwise within
30 minutes to a solution of 500 ml of n-pentylamine in 1.4 l of
methylene chloride while cooling with ice and stirring. After
35 standing at room temperature for 4 hours the reaction solution is
washed in succession with 1 l of 0.1N HCl, 1 l of 0.1N NaOH and
1.5 l of NaCl solution. The organic phase is concentrated on a

rotary evaporator and dried in a high vacuum and gives 370 g of a crystalline mass (98% of theory). M.p. 37°C.

b) N-Pentyl-hexaneiminoyl chloride:

5 81 g of the amide prepared above are dissolved in 800 ml of CCl₄ and treated portionwise with 91 g of phosphorus pentachloride. This mixture is held at reflux temperature for 3 hours, whereby HCl evolves. Now, CCl₄ and POCl₃ are distilled off and finally the product is fractionated in a high vacuum at
10 80-85°C/0.2 mbar. Yield 62 g of a colourless oil (70% of theory). NMR (CDCl₃): 3.44 (t/2H); 2.62 (t/2H); 1.8-1.55 (multiplet/4H); 1.5-1.2 (multiplet/8H); 1.0-0.82 (multiplet/6H).

c) 4-[1-(N-Pentylamino)]-1-hexylidene]-3-methylisoxazol-
15 5(4H)-one: 8 g 3-methylisoxazol-5(4H)-one [prepared according to A.R. Katritzky et al., Tetrahedron 18, 777 (1962)] and 17.9 g of triethylamine are stirred in 320 ml of dioxan for 15 minutes and now treated with 16.5 g of the N-pentyl-hexaneiminoyl chloride prepared above. The reaction mixture is held at reflux
20 temperature for 150 minutes and, after cooling, poured into 800 ml of 2N HCl. Now, the mixture is extracted three times with ether and back-washed with NaCl solution. The organic phase dried over Na₂SO₄, are concentrated and dried in a high vacuum and give 20 g (93%) of a brown mass which is recrystallized in
25 hexane. M.p. 36°C. IR (KBr): 1670; 1620; 1547. NMR (CDCl₃): 10.4 ppm (s,broad/NH); 3.42 (Q/2H); 2.62 (symmetr. multiplet/2H); 2.30 (s/3H); 1.8-1.3 (multiplet/12H); 0.94 (symmetr. multiplet/6H). MS: 266(100%), 223, 209, 112. UV (EtOH): 311 nm (ε = 17900).

30

Example 2

4-[1'-(N-Pentylamino)-1-hexylidene]-3-phenylisoxazol-5(4H)-one

35 The procedure described in Example 1 is repeated, but 3-phenylisoxazol-5(4H)-one [prepared according to A. Hanzsch, Berichte 24, 502 (1891)] is used in section c) in place of 3-methylisoxazol-5(4H)-one. The named product is obtained in 74%

yield as a crystalline powder (m.p. 71°C). (UV EtOH): 314 nm (ϵ = 18000).

Example 3

5

4-[1'-(N-Pentylamino)-1-hexylidenel]-3-n-hexylisoxazol-5(4H)-one

The procedure described in Example 1 is repeated, but 3-n-hexylisoxazol-5(4H)-one is used in section c) in place of 3-methylisoxazol-5(4H)-one. The named product is obtained in 51% yield as a yellowish oil. UV (EtOH): 313 nm (ϵ = 17593).

3-n-Hexylisoxazol-5(4H)-one is obtained in 99% yield as a reddish liquid by holding ethyl 3-oxo-pelargonate at reflux temperature for 1 hour with one equivalent of hydroxylamine hydrochloride and one equivalent of pyridine and thereafter working-up in the usual manner.

20

Example 4

4-[1'-(N-Phenylamino)-1-heptylidenel]-3-methylisoxazol-5(4H)-one

The procedure described in Example 1 is repeated, but in section a) aniline is used in place of n-pentylamine and n-heptanoyl chloride is used in place of caproyl chloride. N-Phenyl-n-heptenamide (m.p. 50°C) is obtained in 94% yield. This is reacted with PCl_5 as in Example 1, section b), and gives in quantitative yield N-phenyl-heptaneiminoyl chloride as a yellowish oil which is converted according to section c) into the desired product and purified by chromatography on silica gel in hexane/ether = 1:1. M.p. 83-84°C. UV (EtOH): 320 nm (ϵ = 19502).

Example 5

4-(2'-Pyrrolidenyl)-3-methylisoxazol-5(4H)-one

2 g of 3-methylisoxazol-5(4H)-one [prepared according to A. Katritzky et al., Tetrahedron 18, 777 (1962)] are treated with 2 g of 2-

methoxy- Δ^1 -pyrroline [prepared according to A.E. Wick et al., *Helv.* 54, 513 (1971)] and left to stand for 2 days. The resulting crystal mass is recrystallized in ethanol and gives white crystals of the desired product in 60% yield. M.p. 188-190°C. UV: 302 nm (ϵ = 18100).

5

Example 6

4-[1'-(N-Isopropylamino)-1-hexylidene]-3-methylisoxazol-5(4H)-one

10 N-isopropyl-caproamide is prepared in the same manner as in Example 1, section a), from caproyl chloride and isopropylamine (yield 80%, b.p. 87°C/0.1 Torr). 11 g thereof are added dropwise to 7 ml of dimethyl sulphate and the mixture is stirred at 25°C for 24 hours. By partition between aqueous potash solution and ether and subsequent
15 concentration and distillation of the organic phase there are obtained 6.7 g (56%) of a yellowish liquid of N-isopropylcaproamide iminomethyl ether (b.p. 50°C/16 Torr). When this iminoether is now held at reflux temperature in an analogous manner to that in Example 1, section c), with one equivalent of 3-methylisoxazol-5(4H)-one and 0.03 equivalent of 1,4-
20 diazabicyclo[2.2.2]octane for 40 hours in toluene, then, after working-up and recrystallization from hexane/ether = 1:1, the desired product is obtained in 20% yield. M.p. 99-101°C, UV (EtOH): 310 nm (ϵ = 17350).

Example 7

25 4-(1'-Amino-1'-dodecylidene)-3-methylisoxazol-5(4H)-one

Gaseous hydrochloric acid is conducted into a solution of 90 g of laurionitrile and 23 g of ethanol while cooling with ice for 60 minutes. A crystalline mass forms after standing for
30 48 hours and this is freed from excess HCl and ethanol on a rotary evaporator. The procedure described in Example 1, section c), is repeated with the crude lauramide iminoethyl ether hydrochloride obtained, i.e. it is added dropwise to a solution of 3-methylisoxazol-5(4H)-one and triethylamine in dioxan and stirred
35 at 25°C for 24 hours. After the usual working-up the desired product is obtained in 98% yield as orange crystals and is

recrystallized from hexane/ethyl acetate = 1:1. M.p. 105-106°C, UV: 302 nm (ϵ = 15000).

Example 8

5

4-(1'-Amino-1'-pentylidene)-3-methylisoxazol-5(4H)-one

When the procedure described in Example 7 is repeated using valeronitrile in place of lauronitrile, then the above product
10 is obtained as a white crystalline powder. M.p. 113-115°C, UV: 302 nm (ϵ = 16270).

Example 9

15

4-(1'-Ethylamino-1'-dodecylidene)-3-methylisoxazol-5(4H)-one

3.6 g of lauronitrile are held at reflux temperature for 24 hours with 7.6 g of triethyloxonium fluoroborate in 20 ml of methylene chloride. Now, the reaction mixture is added dropwise to a solution of 2 g of 3-methylisoxazol-5(4H)-one and 6 g of
20 triethylamine in 60 ml of toluene and the mixture is held at reflux temperature overnight. By partitioning between 2N hydrochloric acid and ether and concentration of the organic phase there is obtained a brown oil which, by purification using chromatography with CH₂Cl₂/methanol = 100:1, gives the desired
25 product as yellow crystals in 60% yield. M.p. 67°C, UV (EtOH): 312 nm (ϵ = 20405).

4(Z)-[1'-(2"-Ethylhexyl)-amino-1'-heptylidene]-3-methylisoxazol-5(4H)-one, (m.p. 0-5°C), is obtained in an analogous
30 manner when there is used as the starting material in place of 4-(1'-amino-1'-dodecylidene)-3-methylisoxazol-5(4H)-one in accordance with Example 7 4-(1'-amino-1'-heptylidene)-3-methylisoxazol-5(4H)-one (m.p. 91°C, prepared with n-heptanonitrile in place of lauronitrile).

35

Likewise, 4(Z)-(1'-hexylamino-2'-methyl-1'-butylidene)-3-methylisoxazol-5(4H)-one is obtained in an analogous manner as a colourless liquid when there is used as the starting material in

place of 4-(1'-amino-1'-dodecylidene)-3-methylisoxazol-5(4H)-one in accordance with Example 7 4-(1'-amino-2'-methyl-1'-butylidene)-3-methylisoxazol-5(4H)-one (m.p. 132°C, prepared with 2-methyl-butyronitrile in place of lauronitrile). [In this
5 latter case, n-hexylamine is used in place of 2-ethyl-1-hexylamine].

Example 10

10 4-[1'-N-(2"-Ethylhexyl)-1'-dodecylidene]-3-methylisoxazol-5(4H)-one

2.8 g of 4-(1'-amino-1'-dodecylidene)-3-methylisoxazol-5(4H)-one, prepared in Example 7, are heated at 100°C for 4 hours with 2 g of 2-ethyl-1-
15 hexylamine, whereby ammonia is liberated. The reaction mixture is partitioned between aqueous NaH₂PO₄ solution and ether and the ether phases are concentrated and filtered over silica gel in hexane/ether = 1:1. 2.9 g (74% yield) of the desired product are obtained as a yellow oil. MS: 392, 293(100%), 265, 154. UV (ethanol): 313 nm (ϵ = 18600).

20 Example 11

4-(1'-N-2-Dodecylaminobenzylidene)-3-methylisoxazol-5(4H)-one

1 g of 4-benzoyl-5-hydroxy-3-methylisoxazole [prepared according to
25 K. Sato et al., Chem. Pharm. Bull 34, 3153 (1986)] is heated at 150°C for 15 minutes with 1 g of n-dodecylamine and thereupon the reaction mixture is partitioned between aqueous NaH₂PO₄ solution and ether. After evaporation of the ether phases the desired product is obtained as a yellow crystalline powder. M.p. 52°C. MS: 370, 369, 341, 215(100%), 185. UV
30 (EtOH): 317 nm (ϵ = 17235).

Example 12

4-(N-n-Dodecylaminomethylidene)-3-methylisoxazol-5(4H)-one

35 3 g of triethyl orthoformate are added to 3.7 g of n-dodecylamine and 2 g of 3-methylisoxazol-5(4H)-one and the reaction mixture is heated at 60°C for 20 hours. Thereupon, it is

filtered over silica gel in hexane/ether/ CH_2Cl_2 = 1:1:3 and the desired product obtained is recrystallized in hexane. Yield 29%, m.p. 57°C , UV (EtOH): 311 nm (ϵ = 18530).

5

Example 134-(p-Isopropylanilino-1'-ethylidene)-3-methylisoxazol-5(4H)-one

3.25 g of triethyl orthoacetate are added to 2.7 g of p-isopropylaniline and 2 g of 3-methylisoxazol-5(4H)-one and the reaction mixture is heated at 80°C for 24 hours. The cooled, crystallized-out reaction mixture is recrystallized in ethanol/ether/hexane/ethyl acetate = 1:1:1:1, whereby the desired product is obtained in 65% yield as yellow crystals. M.p. 170°C , UV (EtOH): 324 nm (ϵ = 21800).

15

Example 144(Z)-(p-n-Hexylanilinomethylidene)-3-hexylisoxazol-5(4H)-one

1.7 g of 3-n-hexylisoxazol-5(4H)-one (prepared in accordance with Example 3) are dissolved in 10 ml of triethyl orthoformate and heated at 80°C for 2 hours together with 2.65 g of p-hexylaniline. The dark reaction solution is concentrated and recrystallized in 100 ml of hexane. 1.8 g (50% of theory) of the above-named crystalline compound are obtained. M.p. $88-90^\circ\text{C}$, UV (EtOH): 356 nm (ϵ = 26469). This compound is especially suitable as a UV A filter.

25

Example 154-[1'-(N-Butylamino)-1'-hexylidene]-3-methylisoxazol-5(4H)-one

a) 4-(1'-Oxy-1'-hexylidene)-3-methylisoxazol-5(4H)-one:
9.9 g of 3-methylisoxazol-5(4H)-one [prepared according to A.R. Katritzky et al., Tetrahedron 18, 777 (1962)] in 200 ml of dichloromethane are treated with 48 g of 4-N,N-dimethylamino-pyridine and subsequently with 16.9 g of caproyl chloride and the mixture is held at reflux temperature for 5 hours. The red coloured reaction solution obtained is partitioned between 1N

35

hydrochloric acid and ethyl acetate and the ethyl acetate phases are back-extracted, dried over Na_2SO_4 and concentrated on a rotary evaporator. A crude oil is obtained in quantitative yield: NMR (CDCl_3): 0.92 (t/3H); 1.38 (multiplet/4H); 1.75 (multiplet/2H);
5 2.36 (s/3H); 2.67 (dxd/2H); 8.9 (s,broad/1H); UV (EtOH): 280 nm (ϵ = 13714).

b) 4-(1'-[N-Butylamino]-1'-hexylidene)-3-methylisoxazol-5(4H)-one:

10 4.9 g of the crude product obtained above are treated with 3.7 g of n-butylamine while cooling and heated at 150°C in an autoclave for 30 minutes. After cooling, the cooled crude product is recrystallized three times from a mixture of methyl tert.butyl ether and hexane, there being obtained 2.8 g (45%) of beige
15 coloured crystals. M.p. $62-63^\circ\text{C}$. UV (EtOH): 312 nm (ϵ = 17980).

Example 16

4(Z)-Ethanolamino-methylidene-3-methylisoxazol-5(4H)-one

20 49.5 g of 3-methylisoxazol-5(4H)-one are dissolved in 125 ml of orthoformic acid and treated slowly at 0°C with 30.5 g of 2-aminoethanol. After stirring for 60 minutes the mixture is cooled to 5°C and the resulting crystals are filtered off under
25 suction and washed with ether. There are thus obtained 60 g of the desired water-soluble product which is recrystallized in methanol. M.p. 135°C , UV (EtOH): 310 nm (ϵ = 17,800). Having regard to the good water solubility, this UV-filter is especially suitable for use in the aqueous phase of sunscreen emulsions.

30

Example 17

Bis-[3-methylisoxazol-5(4H)-ono-4-(1'-ethylidene-1'-amino-2"-propyl-1"-oxy)]-polypropylene glycol ether

35

a) 4-(1'-Ethoxy-1'-ethylidene)-3-methylisoxazol-5(4H)-one:

19.8 g of 3-methylisoxazol-5(4H)-one are dissolved in 50 ml of triethyl orthoacetate and, after 10 minutes, the

resulting crystallizate is filtered off under suction and rinsed with hexane. There are obtained 32.6 g of pale coloured crystals of the desired intermediate. M.p. 126-127°C; UV (EtOH): 294 nm ($\epsilon = 12,000$).

5

b) Bis-[3-methylisoxazol-5(4H)-ono-4-(1'-ethylidene-1'-amino-2"-propyl-1"-oxy)]-polypropylene glycol ether:

8.45 g of the heterocyclic enol ether obtained above are held at reflux temperature for 200 minutes together with 12 g
10 (0.6 equivalents) of polyoxypropylenediamine (BASF; Ludwigshafen, Aetheramin 400; CAS Reg. No. 9046-10-0) in 50 ml of toluene. The reaction mixture is shaken several times between methylene chloride and 1N aqueous sulphuric acid and the organic phases are concentrated. The desired product is
15 obtained as a clear yellowish resin in almost quantitative yield. UV (EtOH): 309 nm ($E = 505$); NMR ($CDCl_3$): 1.1 m/18H(CH_3); 1.3 m/6H(CH_3); 2.3 s/6H(CH_3); 2.4 s/6H(CH_3); 3.3-4.1 m, broad/24H; 10.4 s/2H(NH).

20

Example 18

4(Z)-[1'-(2"-Hydroxyethoxy-2"-ethylamino)-1'-pentylidene]-3-methylisoxazol-5(4H)-one

25 1.8 g of the 4-(1'-amino-1'-pentylidene)-3-methyl- isoxazol-5(4H)-one are heated to reflux temperature in 200 ml of ethanol and treated with 1.58 g of 2-(2'-aminoethoxy)ethanol. After 30 minutes the reaction mixture is cooled and the separated crystals are filtered off under suction and recrystallized in 50 ml
30 of ethanol. There are obtained 1.1 g of white crystals of the desired product. M.p. 100°C; UV (EtOH): 312 nm ($\epsilon = 17709$).

Example 194(Z)-(1'-Ethanol-amino)-1'-heptylidene]-3-methylisoxazol-5(4H)-one

5

9.1 g of the 4-(1'-amino-1'-pentylidene)-3-methylisoxazol-5(4H)-one are heated to 100°C in an autoclave for 2 hours together with 8 equivalents (17.6 g) of ethylene oxide and 40 mg of sodium methylate. The crude product obtained is partitioned
10 between methylene chloride and water, the methylene chloride phase is concentrated and chromatographed over silica gel. There is obtained the desired product as the main component in addition to 4(Z)-[1'-(1"-desoxypolyethyleneglycol-1"-amino)-1'-heptylidene-3-methylisoxazol-5(4H)-one.

15

Example 204(Z)-[p-Potassiumsulphonato-anilinomethylidene]-3-methylisoxazol-5(4H)-one

20

9.9 g of 3-methylisoxazol-5(4H)-one are stirred in 25 ml of triethyl orthoformate for 10 minutes and subsequently treated with 17.3 g of p-sulphanilic acid. After heating to reflux temperature for 15 minutes the mixture is cooled and the
25 resulting crystalline mass is washed with ether and thereupon treated with one equivalent of aqueous KOH and concentrated. There are obtained 16.5 g of yellow crystals of the desired product which still contains sulphanilic acid salt. The pure product is obtained by recrystallization in ethanol. M.p. >240°C.
30 This is a water-soluble UV-A filter. UV (EtOH): 349 nm ($\epsilon = 21513$).

Example 214(Z)-[1'-(2"-Ethyl)-hexylaminomethylidenel]-3-methylisoxazol-5(4H)-one

5

49.5 g of 3-methylisoxazol-5(4H)-one are heated to 75°C in 125 ml of trimethyl orthoformate and treated simultaneously with 64.5 g of 2-ethyl-1-hexylamine and with 23 g of formic acid. After heating to reflux temperature for 2 hours the reaction mixture is partitioned between ice-water and methyl t-butyl ether (MTBE) and the organic phase is concentrated. There are obtained 95.7 g of a red, viscous oil which is recrystallized from MTBE/hexane. M.p. 40°C; UV (EtOH): 312 nm ($\epsilon = 19040$).

15

Example 224(Z)-[1'-N-(2"-Aminopyridino)-1'-ethylidenel]-3-methylisoxazol-5(4H)-one

20

3.3 g of the 4-(1'-ethoxy-1'-ethylidene)-3-methylisoxazol-5(4H)-one prepared in Example 17a) and 1.9 g of 2-aminopyridine are heated to 60°C. Now, the oil bath heating is adjusted to 100°C for 30 minutes. The cooled product is now recrystallized in methylene chloride and diethyl ether. Yield 2.4 g of desired product. M.p. 132°C; UV (EtOH): 342 nm ($\epsilon = 23516$). It is a UV-A filter.

All compounds of the above Examples are novel compounds
I. Preferred derivatives are those of Examples 1, 2, 3, 4, 10, 11,
12, 14, 15, 16, 18, 20, 21.

Example 23

35

A. <u>Oil/water sunscreen lotion</u>	<u>% wt./wt.</u>
A) Compound of Example 1	6.00
Glyceryl myristate	4.00
Cetyl alcohol	0.50

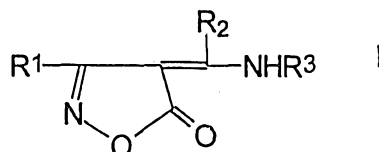
21

	Dimethicone 2)	0.50
	Coco caprylate/caproate 3)	5.00
	Methyl/propylparaben 4)	0.25
	Propylene glycol	2.50
5	Castor oil (hydr.)	2.00
	B) Potassium cetyl phosphate	2.00
	C) Water	74.65
10	Propylene glycol	2.50
	Na ₂ EDTA	<u>0.10</u>
		100.00
	2) (linear dimethylsiloxane polymer)	
15	3) Mixture of esters of coconut alcohol with caprylic acid and caproic acid	
	4) Mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate	
20	B. Oil/water sunscreen cream	
		<u>% wt./wt.</u>
	A) Compound of Example 1	6.00
	Glyceryl stearate	10.00
	PEG-1000 stearate 1)	3.00
25	Isopropyl myristate	3.00
	PEG-7 glyceryl cocoate 2)	6.00
	Methyl/propylparaben	0.25
	B) Water	66.65
30	Na ₂ EDTA	0.10
	Propylene glycol	5.00
	C) Odorant	<u>q.s.</u>
		100.00
35	1) Polyoxyethylene(1000)glycol monostearic acid ester	
	2) Fatty acid glycerol monoester polyethylene(7)glycol ether	

C <u>Oil/water sunscreen cream</u>		
		<u>% wt.%wt</u>
5	A) Cetyl alcohol	1.00
	Glyceryl stearate	4.00
	Dimethicone	0.30
	Coco caprylate/caproate	8.00
	Compound of Example 15	3.00
10	B) Amphisol K	2.00
	C) Water	q.s. to 100
	Carbomer 951 ¹⁾	0.10
	Na ₂ EDTA	0.10
	Methylparaben	0.15
15	D) KOH 10%	0.60
20	E) Phenoxyethanol & methylparaben & ethylparaben & propylparaben	0.35
	F) Odorant	q.s.
25	1) Synthetic polymer from acrylic acid, cross-linked with an allyl ether of pentaerythritol.	

The claims defining the invention are as follows:-

1. A light screening composition which contains a compound of the formula



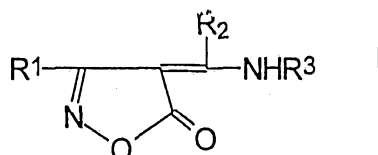
wherein

- 5 R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,
 R² represents H, C₁₋₂₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,
 R³ represents H, C₁₋₁₉-alkyl, C₁₋₁₉-hydroxyalkyl, C₁₋₁₉-polyhydroxyalkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,
 10 or optionally lower alkyl or oxy-lower alkyl substituted pyridyl, a polyether residue, a phenylsulphonic acid residue

and

- R² and R³ together with the N atom can also form a ring; together with an acceptable
 15 carrier, diluent, excipient and/or adjuvant.

2. A light screening composition which contains a compound of the formula



wherein

- 20 R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,
 R² represents H, C₁₋₂₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower-alkyl substituted phenyl,
 R³ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl, or optionally lower-alkyl or oxy-lower alkyl substituted pyridyl,

25 and

- R² and R³ together with the N atom can also form a ring; together with an acceptable carrier, diluent, excipient and/or adjuvant.

3. A light screening composition which contains

- 4-[1-(N-pentylamino)-1-hexylidene]-3-methylisoxazol-5(4H)-one,
 4-[1'-(N-pentylamino)-1-hexylidene]-3-phenylisoxazol-5(4H)-one,
 30 4-[1'-(N-pentylamino)-1-hexylidene]-3-n-hexylisoxazol-5(4H)-one,
 4-[1'-(N-phenylamino)-1-heptylidene]-3-methylisoxazol-5(4H)-one,
 4-[1'-N-(2"-ethylhexyl)-1'-dodecylidene]-3-methylisoxazol-5(4H)-one,

4-[1'-N-(2-dodecylaminobenzylidene)-3-methylisoxazol-5(4H)-one,
 4-(N-n-dodecylaminomethylidene)-3-methylisoxazol-5(4H)-one,
 4-(p-n-hexylanilinomethylidene)-3-hexylisoxazol-5(4H)-one, or
 4-[1'-(N-butylamino)-1'-hexylidene]-3-methylisoxazol-5(4H)-one; together with an

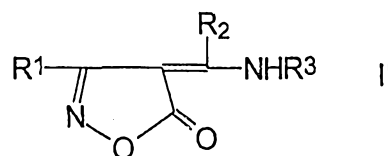
5 acceptable carrier, diluent, excipient and/or adjuvant.

4. A light screening composition which contains
 4-(ethanolamino-methylidene)-3-methylisoxazol-5(4H)-one,
 4-[1'-(2"-hydroxyethoxy-2"-ethylamino)-1'-pentylidene]-3-methylisoxazol-5(4H)-
 one,

10 4-[p-potassium sulphonato-anilinomethylidene]-3-methylisoxazol-5(4H)-one, or
 4-[1'-(2"-ethyl)-hexylaminomethylidene]-3-methylisoxazol-5(4H)-one; together with
 an acceptable carrier, diluent, excipient and/or adjuvant.

5. The composition according to any one of claims 1 to 4, where the carrier,
 diluent, excipient or adjuvant is dermatologically and/or cosmetically acceptable.

15 6. Compounds of the formula



wherein

R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl,

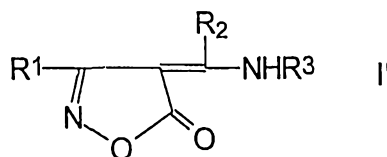
20 R² represents H, C₁₋₂₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or
 oxy-lower alkyl substituted phenyl,

R³ represents H, C₁₋₁₉-alkyl, C₁₋₁₉-hydroxyalkyl, C₁₋₁₉-polyhydroxyalkyl, C₂₋₂₉-
 alkenyl, C₂₋₂₉-alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,
 or optionally lower alkyl or oxy-lower alkyl substituted pyridyl, a polyether residue,
 a phenylsulphonic acid residue

25 and

R² and R³ together with the N atom can also form a ring; and the sum of the carbon
 atoms R¹ + R² + R³ = 9-30 and the number of phenyl residues per molecule does not
 exceed 1.

7. Compounds of the formula



30

wherein

R¹ represents H, C₁₋₁₉-alkyl, C₂₋₂₉-alkenyl, C₂₋₂₉-alkynyl,

R^2 represents H, C_{1-29} -alkyl, C_{2-29} -alkenyl, C_{2-29} -alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl,

R^3 represents H, C_{1-19} -alkyl, C_{2-29} -alkenyl, C_{2-29} -alkynyl, optionally lower-alkyl or oxy-lower alkyl substituted phenyl, or optionally lower alkyl or oxy-lower alkyl substituted pyridyl,

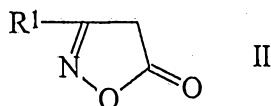
and

R^2 and R^3 together with the N atom can also form a ring; and the sum of the carbon atoms $R^1 + R^2 + R^3 = 9-30$ and the number of phenyl residues per molecule does not exceed 1.

8. A compound selected from
- 4-[1-(N-pentylamino)-1-hexylidene]-3-methylisoxazol-5(4H)-one,
 - 4-[1'-(N-pentylamino)-1-hexylidene]-3-hexylisoxazol-5(4H)-one,
 - 4-[1'-(N-phenylamino)-1-heptylidene]-3-methylisoxazol-5(4H)-one,
 - 4-[1'-N-(2"-ethylhexyl)-1'-dodecylidene]-3-methylisoxazol-5(4H)-one,
 - 4-(1'-N-2-dodecylaminobenzylidene)-3-methylisoxazol-5(4H)-one,
 - 4-(N-n-dodecylaminomethylidene)-3-methylisoxazol-5(4H)-one,
 - 4-(p-n-hexylanilinomethylidene)-3-hexylisoxazol-5(4H)-one, or
 - 4-[1'-(N-butylamino)-1'-hexylidene]-3-methylisoxazol-5(4H)-one.

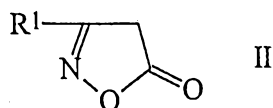
9. A compound selected from
- 4-(ethanolamino-methylidene)-3-methylisoxazol-5(4H)-one,
 - 4-[1'-(2"-hydroxyethoxy-2"-ethylamino)-1'-pentylidene]-3-methylisoxazol-5(4H)-one,
 - 4-[p-potassiumsulphonato-anilinomethylidene]-3-methylisoxazol-5(4H)-one, and
 - 4-[1'-(2"-ethyl)-hexylaminomethylidene]-3-methylisoxazol-5(4H)-one.

10. A process for the manufacture of the compounds of formula I' in accordance with claim 6, which process comprises appropriately substituting an isoxazolone



wherein R^1 has the above significance, in the 4-position.

11. A process for the manufacture of the compounds of formula I' in accordance with claim 7, which process comprises appropriately substituting an isoxazolone of the formula:



wherein R^1 has the above significance, in the 4-position.

12. A compound of the formula I' as set out in claim 6 whenever prepared according to the process of claim 10.

13. A compound of the formula I' as set out in claim 7 whenever prepared according to the process of claim 11.

14. A method of screening light from the surface of a subject in need of such screening, which method comprises administering to said subject an effective amount of a
5 composition according to any one of claims 1 to 4.

Dated 30 March, 1994

Givaudan-Roure (International) SA

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

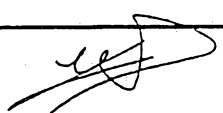


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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 92/00635

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D261/12; A61K7/42; C07D413/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 349 418 (L'OREAL) 3 January 1990 see page 3, line 63 - page 4, line 11; claims 1,9	1,2
A	EP,A,0 199 323 (HOECHST AKTIENGESELLSCHAFT) 29 October 1986 see claim 1	5,6
¹⁰ Special categories of cited documents :¹⁰ "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 "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		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
21 MAY 1992	04. 05. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	HENRY J. C. 	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9200635
SA 57597**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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