(CONVENTION. By one or more persons and/or a Company.) Form 4

COMMONWEALTH OF AUSTRALIA

615219

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

I/We (1) L'OREAL

of 14, rue Royale, 75008 Paris, France

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2) NEW TERT-BUTYL DERIVATIVES OF BENZYLIDENECAMPHOR, PROCESS FOR PREPARING THEM, THEIR USE AS ANTIOXIDANT AGENTS AND COSMETIC AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3) 87008

(3) Here insert number(s) of basic application(s)

for a patent or similar protection made in (4) Luxembourg on 5th October 1987

(4) Here insert Name of basic Country or Countries, and basic date or dates

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 3rd day of October 19 88

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by

(5) L'OREAL

by

MOO-71 04/10/88

(CONVENTION. Company.) Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by(1) L'OREAL

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2) NEW TERT-BUTYL DERIVATIVES OF BENZYLIDENECAMPHOR, PROCESS FOR PREPARING THEM, THEIR USE AS ANTIOXIDANT AGENTS AND COSMETIC AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(3) Here insert full Name and Address, of Company official authorized to make declaration.

I,(3) ANDRE VIOUT

of 14, rue Royale, F-75008 Paris, France

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in(4) Luxembourg

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

on the 5th day of October 19 87, by L'OREAL

~~on the xxx day of xxxx by xxxxx by xxxxx~~

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.(5) GERARD LANG, 44 Avenue Lacour 95210 Saint Gratien, SERGE FORESTIER, 16 Allee Ferdinand Buisson 77410 Claye Souilly, ALAIN LAGRANGE 29 rue Auguste Renoir 78400 Chatou, CLAUDINE MOIRE, 67 Allée Pluton 93600 Aulnay-sous-Bois and ANDRE DEFLANDRE, Route de Manon 60560 Orry la Ville, France

~~is~~/are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of ~~the invention from the said actual~~ inventors

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Paris , France

this 27th day of September 19 88

(12) PATENT ABRIDGMENT (11) Document No. AU-B-23355/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 615219

(54) Title
NEW TERT-BUTYL DERIVATIVES OF BENZYLIDENECAMPHOR, PROCESS FOR PREPARING THEM, THEIR USE AS ANTIOXIDANT AGENTS AND COSMETIC AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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(74) Attorney or Agent
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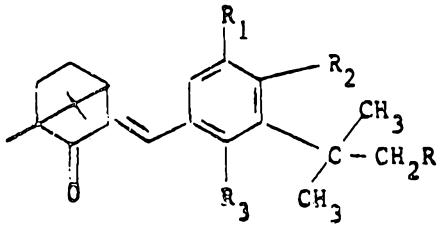
(57) Apart from their good screening properties in the wavelength range extending from 280 to 380 nm, the above compounds simultaneously exhibit, unexpectedly, excellent antioxidant properties with respect to the peroxidation of polyunsaturated lipids, and also with respect to substances capable of undergoing thermo- or photoinduced oxidation reactions (such as, for example, proteins and polymers).

CLAIM

1. A compound having the formula:



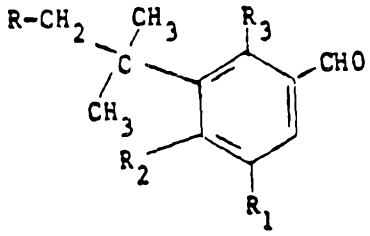
(I)

in which R is hydrogen or a tert-butyl group, R_1 is a C_1-C_8 linear or branched alkyl group or a C_1-C_8 linear or branched alkoxy group; and

R_2 and R_3 are each, independently, hydrogen or a hydroxyl group, with the proviso that at least one of R_2 and R_3 is a hydroxyl group.

.../2

3. A process for preparing a compound of formula (I) according to claim 1 or 2 which comprises performing a condensation reaction between an aromatic aldehyde of formula:



(I)

in which R, R_1, R_2 and R_3 are as defined in claim 1, and synthetic camphor or natural camphor.

18. A process for protecting the skin and natural or sensitized hair against ultraviolet radiation which comprises applying to the skin or hair a composition comprising a compound of formula (I) according to claim 1 or 2 or when prepared by a process according to any one of claims 3 to 8.

32. A method of treating a cancer, skin allergy or inflammation in the human or animal body by therapy or prophylaxis, which comprises administering a compound according to claim 1 or 2 or a composition according to any one of claims ~~26~~ 24 to ~~32~~ 30 by an oral, topical or parenteral route.

N/44758

FORM 10

615219

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

CLASS INT. CLASS

APPLICATION NUMBER:
LODGED:
COMPLETE SPECIFICATION LODGED:
ACCEPTED:
PUBLISHED:

PRIORITY:
RELATED ART:

NAME OF APPLICANT: L'OREAL

ADDRESS OF APPLICANT: 14 rue Royale,
75008 PARIS,
FRANCE.

ACTUAL INVENTOR(S): GERARD LANG, SERGE FORESTIER, ALAIN LAGRANGE, CLAUDINE MOIRE and ANDRE DEFLANDRE.

ADDRESS FOR SERVICE: Edward Waters & Sons
50 Queen Street
Melbourne
Victoria 3000
Australia.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"NEW TERT-BUTYL DERIVATIVES OF BENZYLIDENECAMPHOR, PROCESS FOR PREPARING THEM, THEIR USE AS ANTIOXIDANT AGENTS AND COSMETIC AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention, including the best method of performing it known to us:-

The present invention relates to new tert-butyl derivatives of benzylidenecamphor, to a process for preparing them and to their uses as antioxidant agents as well as in cosmetic compositions for daily use or for protection against sunlight and in pharmaceutical compositions for the preventive treatment of skin allergies and inflammations or certain forms of cancer.

It is well known that the skin is sensitive to solar radiation, which can cause not only ordinary sunburn or erythema, but also more pronounced burns.

However, solar radiation also has other deleterious effects, such as a loss of elasticity of the skin and the appearance of wrinkles leading to premature aging. Sometimes, even dermatoses can also be observed. The extreme case is the occurrence of skin cancers in some subjects.

It is also desirable to provide the hair with good protection against photochemical degradation, in order to avoid a change in hue, a bleaching or a degradation of the mechanical properties.

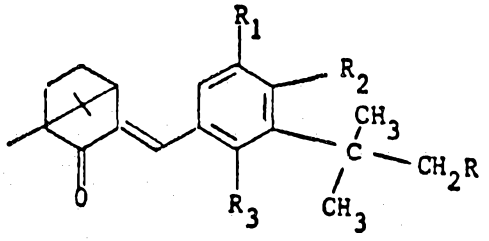
It is known, moreover, that the constituents participating in cosmetic preparations do not always possess sufficient light-fastness, and are degraded

through the action of light radiation.

It is well known that the most dangerous portion of solar radiation consists of ultraviolet radiation of wavelengths of 400 nm and less. It is also known that, as a result of the existence of the ozone layer of the earth's atmosphere, which absorbs a portion of the solar radiation, the lower limit of ultraviolet radiation reaching the earth's surface lies at about 280 nm.

Accordingly, it appears desirable to have recourse to compounds capable of absorbing ultraviolet radiation over a wide band of wavelengths ranging from 280 to 200 nm, that is to say both the UV-B rays of wavelengths from 280 to 320 nm that play a predominant part in the production of solar erythema, and the UV-A rays of wavelengths from 320 to 400 nm that cause not only tanning of the skin but also its aging, and that promote the triggering of the erythemal reaction or that augment that reaction in some subjects or that can even be the source of phototoxic or photoallergic reactions.

According to the present invention benzylidenecamphor derivatives have been found, having the following formula:



(I)

in which:

R is hydrogen or a tert-butyl group,

R_1 is a C_1-C_8 linear or branched alkyl group or a C_1-C_8 linear or branched alkoxy group, and

R_2 and R_3 are each, independently, hydrogen or a hydroxyl group, with the proviso that at least one of R_2 and R_3 is a hydroxyl group.

Apart from their good screening properties in the wavelength range extending from 280 to 380 nm, the above compounds simultaneously exhibit, unexpectedly, excellent antioxidant properties with respect to the peroxidation of polyunsaturated lipids, and also with respect to substances capable of undergoing thermo- or photoinduced oxidation reactions (such as, for example, proteins and polymers).

The peroxidation of lipids involves the formation of intermediate free radicals which damage cell membranes composed, inter alia, of phospholipids, and are responsible, in particular, for phenomena of aging of the skin (A.L. Tappel in "Federation Proceedings" Vol. 32, No. 8, August 1973).

It is extremely advantageous to have recourse to compounds exhibiting both screening properties over a wide band and antioxidant properties boosting the screening effect. Such compounds can make it possible, for example, to combat more satisfactorily the premature aging of the skin due to the peroxidation of cutaneous lipids.

Such compounds can also make it possible to provide for better preservation of cosmetic compositions containing a fatty phase, by preventing the rancidification of the unsaturated lipids present therein. The fatty phase can be of animal origin, such as lanolin, cetin (spermaceti), beeswax, perhydrosqualene or turtle oil, or vegetable origin such as olive oil, castor oil, maize oil, sweet almond oil, avocado oil, shea oil, sunflower oil, soybean oil, groundnut oil or hydrogenated coconut or palm-kernel oils. It can also comprise essential fatty acids such as vitamin F and certain essential oils present in perfumes such as lemon or lavender oil.

In addition, it has been surprisingly found that the compounds of formula (I) as defined above can be used for the preventive treatment of skin allergies and inflammations and also in the prevention of certain cancers.

Apart from their good screening and antioxidant properties, the compounds according to the invention possess an excellent lipid-soluble nature as well as very good thermal and photochemical stability.

These compounds generally also have the advantage of not being toxic or irritant and of being completely safe with respect to the skin.

They can be distributed uniformly in traditional cosmetic vehicles capable of forming a continuous film and,

in particular, in fatty vehicles, and can thus be applied on the skin to form an effective protective film.

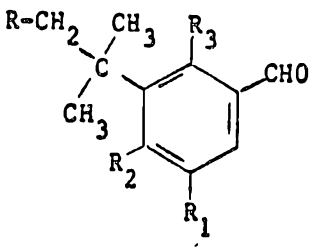
The present invention accordingly provides compounds of formula (I) above.

In this formula, R_1 can be, for example, a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl or 1,1,3,3-tetramethylbutyl group or alternatively a methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy group.

Examples of compounds of general formula (I), include:

- 3'-tert-butyl-2'-hydroxy-5'-methoxy-3-benzylidene-dl-camphor,
- 3'-tert-butyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor,
- 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidene-d-camphor,
- 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidene-dl-camphor,
- 3',5'-di-tert-butyl-2'-hydroxy-3-benzylidene-dl-camphor, and
- 3'-tert-octyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor.

The compounds of formula (I) can be obtained by performing a condensation reaction between synthetic camphor (dl-camphor) or natural camphor (d-camphor) and an aromatic aldehyde of formula:



(III)

R, R_1, R_2 and R_3 having the definitions above.

The aldehydes of formula (III) are prepared according to known methods.

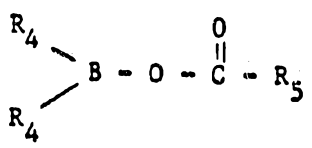
The condensation of the aldehyde (III) with camphor may be performed according to one of the following two processes:

1st Process:

The condensation is performed under reflux in an organic solvent in the presence of a base. The base is suitably an alkali metal alcoholate such as sodium methylate or potassium tert-butylate, and the solvent is suitably toluene. It is also suitable to use an inorganic base such as an alkali metal amide or hydride and a solvent such as dimethoxyethane.

2nd Process:

The condensation of the aldehyde (III) with camphor is performed in the presence of a borane of the following formula (IV):



(IV)

in which R_4 is a C_1-C_6 alkyl group and R_5 is a C_1-C_4 alkyl group. This compound is obtained according to the procedure described by L.H. Toporcer et al., J. Am. Chem. Soc. 87, 1236 (1965). Its isolation and purification are not necessary in order to carry out the condensation of the aldehyde (III) with camphor.

The condensation reaction is performed at a temperature of from 140°C to 160°C and a solvent is not essential.

The present invention therefore also provides a process for preparing the compounds of formula (I).

In addition, the present invention provides a composition suitable for cosmetic use comprising an effective amount of at least one benzylidenecamphor derivative of formula (I) above, in a cosmetically acceptable vehicle comprising at least one fatty phase.

The composition of the invention is suitable for application to the human epidermis or the hair, or for use as an antisun composition.

The present invention also provides a process for protecting the skin and natural or sensitized hair against solar radiation, which comprises applying to the skin or hair an effective amount of at least one compound of formula (I) contained in a cosmetically acceptable vehicle containing at least one fatty phase.

"Sensitized hair" is understood to mean hair which has undergone a permanent-waving, dyeing or bleaching treatment.

The invention further provides a coloured or uncoloured cosmetic composition, stabilized to light and/or oxidation, comprising an effective amount of at least one benzylidenecamphor derivative of formula (I) above.

When used, a composition suitable for protecting the human epidermis against ultraviolet rays, the cosmetic composition according to the invention is generally presented in the most diverse forms customarily used for this type of composition. It is suitably presented in the form of oily or oleoalcoholic lotion, of emulsions such as a cream or a milk, of oleoalcoholic, alcoholic or aqueous-alcoholic gels, or of solid sticks, or is packaged as an aerosol.

It suitably comprises at least one cosmetic adjuvant customarily used in this type of composition, such as a thickener, emollient, humectant, surfactant, preservative, antifoam, perfume, oil, wax, lanolin, propellant, colourings and/or pigment whose function is to colour the composition itself or the skin, or any other ingredient customarily used in cosmetics.

The compound of formula (I) is generally present in a proportion by weight of from 0.1 to 2% relative to the total weight of the cosmetic composition for protecting

the human epidermis.

Suitable solubilization solvents include oil, wax and, generally speaking, any fat, a monohydric alcohol or a lower polyol or a mixture thereof. Examples of suitable monohydric alcohols or polyols include ethanol, isopropanol, propylene glycol, glycerin and sorbitol.

One embodiment of the invention is an emulsion in the form of a protective cream or milk comprising, in addition to the compound of formula (I), a fatty alcohol, fatty acid ester and, in particular, a fatty acid triglyceride, fatty acid, lanolin, natural or synthetic oil or wax, or emulsifier, in the presence of water.

Another embodiment comprises an oily lotion based on natural or synthetic oils and waxes, lanolin and fatty acid esters, in particular fatty acid triglycerides; or an oleoalcoholic lotion based on a lower alcohol such as ethanol or a glycol such as propylene glycol and/or a polyol such as glycerin, and oils, waxes and fatty acid esters such as fatty acid triglycerides.

The cosmetic composition of the invention is also suitably an alcoholic gel comprising one or more lower polyols or alcohols such as ethanol, propylene glycol or glycerin, and a thickener such as silica. The oleoalcoholic gels comprise, in addition, a natural or synthetic oil or wax.

The solid sticks consist of natural or synthetic

oils and waxes, fatty alcohols, fatty acid esters, lanolin and other fats.

The present invention also provides an antisun cosmetic composition comprising at least one compound of formula (I) and, optionally, at least one other UV-B or UV-A screening compound, or a combination thereof.

The amount of compound of formula (I) present in the antisun composition is generally from 0.2 to 15% by weight relative to the total weight of the antisun composition, the total amount of screening compounds generally being from 0.5 to 15% by weight.

When the composition is packaged as an aerosol, traditional propellants are used, such as alkanes, fluoroalkanes and chlorofluoroalkanes.

When the cosmetic composition according to the invention is presented in a form suitable for protecting natural or sensitized hair from UV rays, it is generally a shampoo, a lotion, gel or emulsion to be rinsed, to be applied before or after shampooing, before or after dyeing or bleaching, or before or after permanent-waving, a styling or treating lotion or gel, a lotion or gel for blow-drying or setting, a hair lacquer, or a composition for permanent-waving, dyeing or bleaching the hair. Such a composition suitably comprises at least one additional adjuvant commonly used in this type of composition, such as a surfactant, thickener, polymer, emollient, perservative,

foam stabilizer, electrolyte, organic solvent, silicone derivative, oil, wax, antigrease agent, colouring and/or pigment whose function is to colour the composition itself or the hair, or any other ingredient customarily used in the hair-care field.

It generally comprises from 0.25 to 2% by weight of compound of formula (I).

The present invention provides, in addition, a cosmetic composition comprising at least one compound of formula (I) as an agent for protection against ultraviolet rays and as an antioxidant. Examples include hair-care compositions such as hair lacquers, hair-setting lotions optionally having treating or disentangling properties, shampoos, colouring shampoos and hair dyeing compositions, makeup products such as nail varnishes, treatment creams and oils for the epidermis, makeup foundations, lipsticks and skin care compositions such as bath oils or creams, as well as any other cosmetic composition which, as a result of its constituents, displays problems of light-fastness and/or stability to oxidation during storage.

Such compositions generally comprise from 0.1 to 2% by weight of compound of formula (I).

The invention further provides a process for protecting a cosmetic composition against ultraviolet rays and oxidation, which comprises incorporating an effective amount of at least one compound of formula (I) in such a

composition.

The invention also provides the use of the compounds of formula (I) as antioxidants.

The invention also provides the use of a compound of formula (I) as a broad-band sunscreen absorbing in the wavelength range extending from 280 to 380 nm.

The invention further provides the application of a compound of formula (I) as a cosmetic product.

It has been found, in addition, that compounds of formula (I) exhibit advantageous pharmacological activity in the treatment by therapy or prophylaxis of skin allergies and inflammations, and certain cancers.

The present invention therefore provides a compound of formula (I) for use in a method of treatment of the human or animal body by surgery or therapy, or in a method of diagnosis practised on the human or animal body.

Accordingly, it also provides a method of treating a cancer, skin allergy or inflammation by therapy or prophylaxis, which comprises administering a compound of formula (I) or a composition comprising the said compound by an oral, topical or parenteral route.

The invention further provides a composition which comprises, in a pharmaceutically acceptable excipient or vehicle, an effective amount of a compound of formula (I).

The pharmaceutical composition according to the invention is suitably administered orally or topically.

For oral administration, the pharmaceutical composition is generally presented in the form of tablets, hard gelatin capsules, dragees, a syrup, suspension, solution, emulsion, and the like. For topical administration, the pharmaceutical composition according to the invention is generally presented in the form of an ointment, cream, pomade, solution, lotion, gel, spray, suspension and the like.

The pharmaceutical composition suitably comprises at least one inert or pharmacodynamically active additive, for example a moisturizing agent, antibiotic, steroidal or non-steroidal anti-inflammatory agent, carotenoid or antipsoriatic agent.

The composition also suitably comprises a flavour-improving agent, preservative, stabilizing agent, moisture-regulating agent, pH-regulating agent, osmotic pressure-modifying agent, emulsifying agent, local anaesthetic, buffer, and the like.

It is suitably packaged in a delay or sustained-release form.

The compound of formula (I) according to the invention is present in the pharmaceutical compositions in a proportion of from 0.01 to 80% by weight relative to the total weight of the composition, for example from 0.1 to

20% by weight.

In the therapeutic application, the treatment is determined by the doctor. The dose of active ingredient will vary according to the patient's age, weight and response, as well as to the severity of the symptoms.

When the compounds of formula (I) are administered orally, the dosage is generally from 0.1 to 50 mg/kg/day, for example from 0.2 to 20 mg/kg/day. The treatment period is variable, depending on the severity of the symptoms, and extends, for example, from 1 to 25 weeks, continuously or discontinuously.

The compositions for topical administration generally comprise from 0.25% to 4% by weight of compound of formula (I).

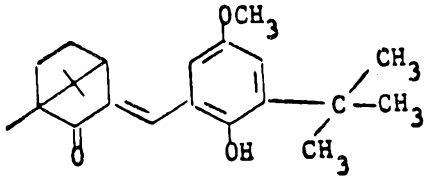
As vehicle or excipient for the pharmaceutical composition of the invention, all non-toxic conventional vehicles or excipients are suitable.

The examples which follow further illustrate the invention.

PREPARATION EXAMPLES

EXAMPLE 1

Preparation of 3'-tert-butyl-2'-hydroxy-5'-methoxy-3-benzylidene-dl-camphor of formula:



21 g (0.138 mol) of dl-camphor are dissolved in 100 cm^3 of dimethoxyethane dried over a 4 Å molecular sieve. 6.35 g (0.276 mol) of sodium hydride are added and the mixture is heated under reflux for one hour.

24 g (0.115 mol) of 3-tert-butyl-2-hydroxy-5-methoxybenzaldehyde, dissolved in 80 cm^3 of 1,2-

dimethoxyethane, are added dropwise. The mixture is heated under reflux for 3 hours. After being cooled, the reaction mixture is poured into water. The mixture is acidified by adding 10% strength hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized in absolute ethanol.

12.35 g (31%) of expected product are obtained, possessing the following characteristics:

- appearance : yellow crystals
- melting point : 223°C
- elemental analysis : $C_{22}H_{30}O_3$

	C%	H%	O%
Calculated	77.15	8.83	14.01
Found	76.87	8.83	13.88

- UV spectrum (methanol):

λmax_1 = 297 nm $\quad \varepsilon$ = 15700

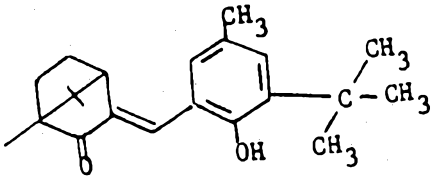
λmax_2 = 365 nm $\quad \varepsilon$ = 10460

- ^1H NMR Spectrum (80 MHz) ($CDCl_3$ + DMSO-d_6):

in agreement with the expected structure.

EXAMPLE 2

Preparation of 3'-tert-butyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor



This compound is obtained according to the procedure described in Example 1, in which 3-tert-butyl-2-hydroxy-5-methoxybenzaldehyde is replaced by 3-tert-butyl-2-hydroxy-5-methylbenzaldehyde.

The product obtained possesses the following characteristics:

- appearance : yellow crystals
- melting point : 213°C
- elemental analysis : $C_{22}H_{30}O_2$

	C%	H%	O%
Calculated	81.18	8.98	9.83
Found	81.39	9.04	9.92

- UV spectrum (methanol)

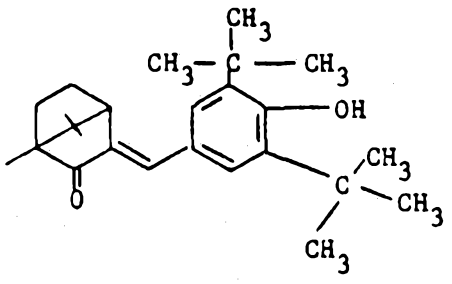
  λ max$_1$ = 295 nm ϵ = 14600

  λ max$_2$ = 335 nm ϵ = 8470

- ^{1}H NMR Spectrum (80 MHz) ($CDCl_3$ + DMSO-d_6): in agreement with the expected structure.

EXAMPLE 3

Preparation of 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidenecamphor



a) 1st method of synthesis: (derived from natural camphor)

50 g (0.328 mol) of d-camphor are dissolved in

400 cm^3 of 1,2-dimethoxyethane. 17.5 g of sodium hydride (0.73 mol) are added and the mixture is brought to reflux for one hour. 70 g (0.3 mol) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde are added and the mixture is heated under reflux for 10 hours. After being cooled, the reaction medium is gradually diluted with 100 cm^3 of ethanol and then with 100 cm^3 of water. The mixture is acidified by adding 10% strength hydrochloric acid. The precipitate formed is filtered off, washed with water and dried. After recrystallization in isopropyl ether and then in ethanol, 54.5 g (49% yield) of expected product are obtained, possessing the following characteristics:

- appearance : white crystals
- melting point : 186°C
- elemental analysis $C_{25}H_{36}O_2$

	C%	H%	O%
Calculated	81.47	9.84	8.68
Found	81.40	9.87	8.79

- UV spectrum (chloroform)

  λ max : 325 nm ϵ = 23000

- ^1H NMR Spectrum (80 MHz) ($CDCl_3$ + DMSO-d_6):

  in agreement with the expected structure.

b) <u>2nd method of synthesis</u>: (derived from synthetic camphor)

41 g (0.4 mol) of pivalic acid are added at 0°C to 500 cm^3 of a 1M solution of triethylborane in hexane. After 15 min of stirring at 0°C, the mixture is allowed

to return to room temperature, and 28 g (0.19 mol) of dl-camphor and 44.5 g (0.19 mol) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde are then added.

The hexane is distilled off and the mixture is heated to 150-160°C for 3 hours. The volatile products are distilled off under reduced pressure (1995 Pa.s, then 13 Pa.s).

The reaction mixture is diluted with 200 cm^3 of ethyl acetate. The organic phase is washed with water and then dried. The solvent is distilled off under reduced pressure. After recrystallization in isopropyl ether, 50.1 g (72% yield) of expected product are obtained, possessing the following characteristics:

- appearance : white crystals
- melting point : 158°C
- elemental analysis : $C_{25}H_{36}O_2$

	C%	H%	O%
Calculated	81.47	9.84	8.68
Found	81.37	9.84	8.78

- UV spectrum (chloroform)

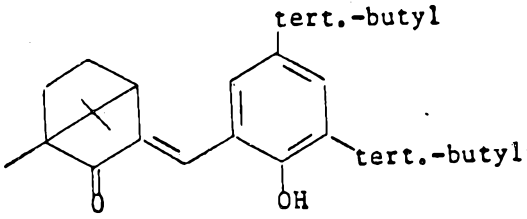
λ max = 323 nm ϵ = 24200

- ^1H NMR Spectrum (80 MHz) ($CDCl_3$ + DMSO-d_6):

in agreement with the expected structure.

EXAMPLE 4

Preparation of 3',5'-di-tert-butyl-2'-hydroxy-3-benzylidene-dl-camphor of formula:



This compound is obtained according to the procedure described in Example 1, in which 3-tert-butyl-2-hydroxy-5-methoxybenzaldehyde is replaced by 3,5-di-tert-butyl-2-hydroxybenzaldehyde.

The product obtained possesses the following characteristics:

- Melting point : 220°C
- Elemental analysis : $C_{25}H_{36}O_2$

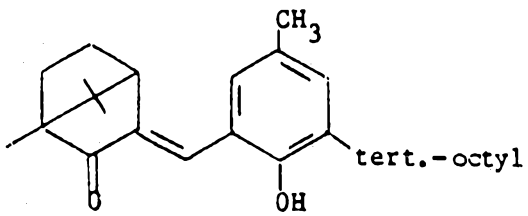
	C%	H%	O%
Calculated	81.47	9.85	8.68
Found	81.29	9.79	8.89

- UV spectrum (dichloromethane)
  - . λ max$_1$: 292 nm
  - . ϵ_1 : 13000
  - . λ max$_2$: 330 nm
  - . ϵ_2 : 7500
- ^{1}H NMR Spectrum (80 MHz) ($CDCl_3$ + DMSO-d_6):

  in agreement with the expected structure.

EXAMPLE 5

Preparation of 3'-tert-octyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor of formula:



This compound is obtained according to the procedure described in Example 1, in which 3-tert-butyl-2-hydroxy-5-methoxybenzaldehyde is replaced by 3-tert-octyl-2-hydroxy-5-methylbenzaldehyde.

The product obtained possesses the following characteristics:

- Melting point : 176°C
- Elemental analysis : $C_{26}H_{38}O_2$

	C%	H%	O%
Calculated	81.62	10.01	8.36
Found	81.84	9.95	8.51

- UV spectrum (dichloromethane)
  - λ max$_1$: 293 nm
  - ϵ_1 : 12000
  - λ max$_2$: 335 nm
  - ϵ_2 : 6460
- ^{1}H NMR Spectrum (80 MHz) ($CDCl_3$ + DMSO-d_6): in agreement with the expected structure.

APPLICATION EXAMPLES

Example 1 - Antisun oil

The following ingredients are mixed, optionally heating to 40-45°C in order to homogenize:

Compound of Example 3	0.6 g
Benzoate of C_{12}-C_{15} alcohols, sold by FINETEX under the name "FINSOLV TN"	30.0 g
Sunflower oil	20.0 g
Perfume	1.0 g

Cyclic dimethylpolysiloxane sold by UNION CARBIDE under the name "VOLATILE SILICONE 7207" qs 100 g

The compound of Example 3 may be replaced by that of Example 4

Example 2 - Gel for protecting the skin

The following gel is prepared:

Compound of Example 3	0.12 g
Polyacrylic acid crosslinked with a polyfunctional agent, sold by the company GOODRICH under the name "CARBOPOL 934"	0.8 g
Glycerin	12.0 g
Ethanol	15.0 g
Preservative	0.2 g
Perfume	0.2 g
Triethanolamine qs pH 5.3	
Demineralized water qs	100 g

The screening compound is dissolved in the ethanol/glycerin mixture; the water, preservative and perfume are added. In this aqueous phase, the Carbopol is dispersed homogeneously and the pH is adjusted to 5.3 with triethanolamine.

Example 3 - Antisun stick

The following solid stick is prepared:

Compound of Example 3	1.0 g
Ozocerite "SP 1020" (STRAHL & PITSCH)	20.0 g

Beeswax	7.0 g
Oleyl alcohol	12.0 g
Hydrogenated lanolin "HYDROLAN H" (ONYX CHEMICAL)	8.0 g
Lanolin oil "ARGONOL 60" (WESTBROOK LANOLIN)	8.0 g
Carnauba wax	1.0 g
Benzoate of C_{12}-C_{15} alcohols "FINSOLV TN" (FINETEX)	17.0 g
Octamethylcyclotetrasiloxane "ABIL K4" (GOLDSCHMIDT)	3.0 g
Liquid paraffin qs	100. g

The various compounds are melted at about 70-75°C so as to obtain a liquid phase in which the screening compound is dissolved. This solution is poured into moulds and allowed to cool.

Example 4 - Antisun milk

Compound of Example 3	0.25 g
Benzylidenecamphor	2.0 g
Mixture of fatty acid esters, polyglycerolated esters and silicone-based surfactants "ABIL WS08" (GOLDSCHMIDT)	5.0 g
White vaseline	2.0 g
Beeswax	2.5 g
Benzoate of C_{12}-C_{15} alcohols "FINSOLV TN" (FINETEX)	19.0 g
Glycerin	5.0 g

Sodium chloride	2.0 g
Perfume	0.4 g
Preservative	0.2 g
Demineralized water qs	100. g

This is a water-in-oil emulsion. The screening compounds are dissolved in the fat and the emulsifier and the mixture is heated to 70-80°C; the aqueous phase consisting of the water, sodium chloride and glycerin is heated to the same temperature; the aqueous phase is added to the fatty phase with brisk stirring, the mixture is then allowed to cool with moderate stirring and to about 40°C, and perfume and preservative are added.

Example 5 - Antisun milk

Compound of Example 3	1.5 g
2-Ethylhexyl p-methoxycinnamate "PARSOL MCX" (GIVAUDAN)	3.5 g
2-Hydroxy-4-methoxybenzophenone "UVINUL M40"	1.0 g
Cetyl alcohol	1.0 g
Oleocetyl alcohol containing 30 mol of ethylene oxide "MERGITAL OC 30" (HENKEL)	5.0 g
Stearyl alcohol	4.0 g
Synthetic oil of formula: $C_{15}H_{31}COOCH_2-\underset{\underset{OH}{|}}{CH}-CH_2OCH_2-\underset{\underset{C_2H_5}{|}}{CH}-C_4H_9$	2.0 g
90:10 Mixture of cetostearyl 2-ethylhex-	

anoate and isopropyl myristate "CERAMOLL"		
(Créations Aromatiques)		2.0 g
Liquid paraffin		8.0 g
Propylene glycol		4.0 g
Preservative		0.2 g
Perfume		0.4 g
Demineralized water	qs	100. g

This is an oil-in-water emulsion. The screening compounds are dissolved in the fats at about 70°-80°C; the aqueous phase consisting of the water, propylene glycol and emulsifier is heated to the same temperature, and the fatty phase is added to the aqueous phase with brisk stirring, the mixture is then allowed to cool with moderate stirring and preservative and perfume are added at about 40°C.

Example 6 - Antisun cream

The following cream, forming an oil-in-water emulsion, the aqueous phase of which consists of water, sorbitol, sodium lactate and emulsifier and in which {4-[(2-oxo-3-bornylidene)methyl]phenyl}trimethylammonium methylsulphate is dissolved, is prepared in the same manner as in Example 5:

Compound of Example 3	0.5 g
{4-[(2-Oxo-3-bornylidene)methyl]-phenyl}-trimethylammonium methylsulphate	4.0 g
Sodium lactate, 60% pure	1.0 g
Mixture of cetyl stearyl alcohol and	

cetylstearyl alcohol oxyethylenated with 33 mol of ethylene oxide "SINNOWAX AO" (HENKEL)		7.5 g
Cetyl alcohol		1.0 g
Myristyl alcohol "SIPOL C14" (HENKEL)		0.6 g
Sorbitol, 70% pure		3.0 g
Isopropyl palmitate		10.0 g
Liquid paraffin		7.0 g
Preservative		0.2 g
Perfume		0.6 g
Demineralized water	qs	100. g

Example 7 - Antisun oil

The following ingredients are mixed, optionally heating to 40-45°C in order to homogenize:

Compound of Example 2		0.2 g
p-Methylbenzylidenecamphor		2. g
Perfume	qs	
Isopropyl myristate	qs	100. g

The compound of Example 2 may be replaced by that of Example 5.

In Examples 8 and 9 below, the compounds of the invention are used as antioxidants in order to prevent rancidification of the compositions.

Example 8 - Care cream

The following cream, forming a water-in-oil emulsion, the aqueous phase of which comprises water, ascorbic acid, EDTA, glutathione and citric acid, is

prepared in the same manner as in Example 4:

Magnesium lanolate	14.4 g
Lanoline alcohol	3.6 g
Sunflower oil	40.0 g
Isopropyl myristate	8.0 g
Ozocerite	4.0 g
Vitamin F	2.0 g
Ascorbic acid	0.5 g
Soybean lecithin	5. g
Compound of Example 3	0.25 g
Ascorbyle palmitate	1.0 g
Glutathione	0.1 g
N-Acetylcysteine	0.05 g
Citric acid	0.05 g
Ethylenediaminetetraacetic acid (EDTA)	0.15 g
Perfume	0.8 g
Methyl para-hydroxybenzoate	0.3 g
Water qs	100. g

Example 9 - Face and body oil

The following ingredients are mixed, optionally heating to 40-45°C in order to homogenize:

Shea oil	2.0 g
Sunflower oil	31.8 g
Vitamin F	2.0 g
Soybean oil	32.0 g
Compound of Example 1	0.1 g
Citric acid	0.05 g

Ascorbyl palmitate	1.0	g
N-Acetylcysteine	0.1	g
Ethylenediaminetetraacetic acid (EDTA)	0.15	g
Soybean lecithin	0.1	g
Groundnut oil qs	100.	g

Pharmaceutical compositions used topically:

Example 10 - Soothing ointment

(To be applied on irritated skin in order to bring relief)

Compound of Example 3	2.00	g
Fluid paraffin oil	9.10	g
Silica sold by the company DEGUSSA under the name "AEROSIL 200"	9.20	g
Isopropyl myristate qs	100.	g

Example 11 - Anti-inflammatory (oil-in-water) cream

Compound of Example 4	3.00	g
Sodium dodecyl sulphate	0.80	g
Glycerol	2.00	g
Stearyl alcohol	20.00	g
Triglycerides of capric/caprylic acids, sold by the company DYNAMIT NOBEL under the name "MIGLYOL 812"	20.00	g
Preservatives qs		
Demineralized water qs	100.	g

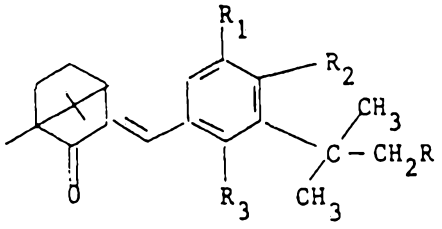
Example 12 - Soothing gel

Compound of Example 5	1.00	g
Hydroxypropyl cellulose sold by the		

company HERCULES under the name		
"KLUCEL HF"		2.00 g
Ethanol		70.00 g
Water	qs	100. g

The claims defining the invention are as follows:

1. A compound having the formula:



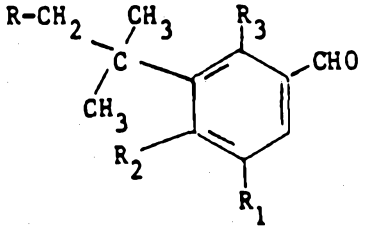
(I)

in which R is hydrogen or a tert-butyl group, R_1 is a C_1-C_8 linear or branched alkyl group or a C_1-C_8 linear or branched alkoxy group; and

R_2 and R_3 are each, independently, hydrogen or a hydroxyl group, with the proviso that at least one of R_2 and R_3 is a hydroxyl group.

2. A compound according to claim 1 which is 3'-tert-butyl-2'-hydroxy-5'-methoxy-3-benzylidene-dl-camphor, 3'-tert-butyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor, 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidene-d-camphor, 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidene-dl-camphor, 3',5'-di-tert-butyl-2'-hydroxy-3-benzylidene-dl-camphor or 3'-tert-octyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor.

3. A process for preparing a compound of formula (I) according to claim 1 or 2 which comprises performing a condensation reaction between an aromatic aldehyde of formula:



(III)

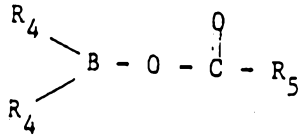
in which R, R_1, R_2 and R_3 are as defined in claim 1, and synthetic camphor or natural camphor.

4. A process according to claim 3 in which the condensation reaction is performed under reflux in an organic solvent, in the presence of a base.

5. A process according to claim 4 in which the base is sodium methylate or potassium tert-butylate and the organic solvent is toluene.

6. A process according to claim 4 in which the base is an alkali metal amide or hydride and the organic solvent is dimethoxyethane.

7. A process according to claim 3 in which the condensation reaction is performed in the presence of a borane of formula:



(IV)

in which R_4 is a C_1-C_6 alkyl group and R_5 is a C_1-C_4 alkyl group, at a temperature of 140 to 160°C.

8. A process according to any one of claims 3 to 7 and substantially as decribed in any one of Preparation Examples 1 to 5.

9. A composition suitable for cosmetic use which comprises a compound of formula (I) according to claim 1 or 2 or when prepared by a process according to any

one of claims 3 to 8, in a cosmetically acceptable vehicle comprising at least one fatty phase.

10. A composition according to claim 9 which comprises at least one of 3'-tert-butyl-2'-hydroxy-5'-methoxy-3-benzylidene-dl-camphor, 3'-tert-butyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor, 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidene-d-camphor, 3',5'-di-tert-butyl-4'-hydroxy-3-benzylidene-dl-camphor, 3',5'-di-tert-butyl-2'-hydroxy-3-benzylidene-dl-camphor or 3'-tert-octyl-2'-hydroxy-5'-methyl-3-benzylidene-dl-camphor.

11. A composition according to claim 9 or 10 which is in the form of an oily or oleoalcoholic lotion, an emulsion, an oleoalcoholic, alcoholic or aqueous-alcoholic gel, a solid stick or an aerosol.

12. A composition according to claim 11, which comprises a cosmetic adjuvant which is a thickener, emollient, humectant, surfactant, preservative, antifoam, perfume, oil, wax, lanolin, lower polyol or monohydric alcohol, propellant, colouring or pigment.

13. A composition according to any one of claims 9 to 12 which is suitable for application to the human epidermis or to the hair and comprises from 0.1 to 2% by weight of a compound of formula (I).

14. A composition according to any one of claims 9 to 13 which is in the form of a shampoo, lotion, gel or

emulsion to be rinsed, styling or treating lotion or gel, lotion or gel for blow-drying or setting, hair lacquer or composition for permanent-waving, bleaching or dyeing, and comprises from 0.25 to 2% by weight of compound of formula (I).

15. A composition according to any one of claims 8 to 11 which is in the form of an antisun composition and which comprises from 0.2 to 15% by weight of compound of formula (I).

16. A composition according to claim 15 which comprises an agent screening UV-B or UV-A rays or a mixture thereof.

17. A composition according to any one of claims 9 to 16 and substantially as described in any one of Application Examples 1 to 9.

18. A process for protecting the skin and natural or sensitized hair against ultraviolet radiation which comprises applying to the skin or hair a composition comprising a compound of formula (I) according to claim 1 or 2 or when prepared by a process according to any one of claims 3 to 8.

19. A process for protecting a cosmetic composition against ultraviolet rays or oxidation which comprises incorporating into the composition at least one compound of formula (I) according to claim 1 or 2 or when prepared by a process according to any one of claims 3 to

8.

20. A composition protected against ultraviolet rays or oxidation when produced by a process according to claim 19.

21. A compound of formula (I) according to claim 1 or 2 for use in a method of treatment of the human or animal body by surgery or therapy, or in a method of diagnosis practised on the human or animal body.

22. A compound according to claim 21 for use in the preventive treatment of skin allergies and inflammations.

23. A compound according to claim 22 for use in the prevention of certain cancers.

24. A composition which comprises, in a pharmaceutically acceptable excipient or vehicle, at least one compound of formula (I) according to claim 1 or 2 or when prepared by a process according to any one of claims 3 to 8.

25. A composition according to claim 24, suitable for topical administration, in the form of a cream, ointment, pomade, solution, gel, lotion, spray or suspension.

26. A composition according to claim 24 ~~25~~ suitable for oral administration, in the form of tablets, hard gelatin capsules, dragees, a syrup, suspension, solution or emulsion.

27. A composition according to claim 25 ~~26~~, wherein the active compound of formula (I) is present in a proportion of from 0.25 to 4% by weight relative to the total weight of the composition.

28. A composition according to claim 26 ~~27~~, which comprises the active ingredient in a proportion suitable for administration at a dose of from 0.1 to 50 mg/kg/day.

29. A composition according to claim 28 in which the dose is from 0.2 to 20 mg/kg/day.

30. A composition according to any one of claims 25 and 27 24, ~~to 29~~ substantially as hereinbefore described in any one of Application Examples 10 to 12.

31. A compound of formula (I) as defined in claim 1 or 2 whenever produced by a process according to any one of claims 3 to 8.

32. A method of treating a cancer, skin allergy or inflammation in the human or animal body by therapy or prophylaxis, which comprises administering a compound according to claim 1 or 2 or a composition according to any one of claims ~~26~~ 24 to 30 ~~32~~ by an oral, topical or parenteral route.

33. A method according to claim 32 wherein the active compound is administered orally at a dose of from 0.1 to 50 mg/kg/day.

34. A method according to claim 32 wherein the active compound is administered topically in a composition comprising from 0.25 to 4% by weight of active ingredient.

DATED this 3rd day of October 1988.
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