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COMPOSITIONS CONTAINING COUMARIN ETHER SUN-SCREENING COMPOUNDS

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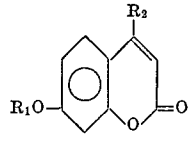
Int. Cl. A61k 9/06; A61l 23/00
U.S. Cl. 424—59 3 Claims

ABSTRACT OF THE DISCLOSURE

Sun-screening compositions containing essentially colorless, stable, odorless, non-irritating, non-sensitizing, and oil-compatible coumarin ether compounds, such compounds having the formula:



wherein R_1 is alkenyl, cycloalkenyl, alkadienyl, cycloalkadienyl, alkatrienyl, alkoxyalkadienyl, acyloxyalkadienyl, alkoxyalkenyl, cyclialkoxyalkenyl, aryl, alkaryl, or aralkyl and R_2 is hydrogen or lower alkyl and such compounds having ultraviolet absorption maxima within the range of 2,900 A. up to about 3,400 A.

This application is a division of applicant's copending parent application Ser. No. 883,239, filed on Dec. 9, 1969, now U.S. Pat. 3,625,976.

The invention relates to compositions containing specific sun-screen compounds; to methods for protecting the human skin against the burning, tanning and degradation effects of sunlight, to certain new and useful sun-screen compounds, and in particular to cosmetic compositions incorporating the compounds including the novel compounds of this invention which are outstandingly useful for protecting the skin against sunlight.

No one material possessing all of the desirable characteristics of sun screening compounds including: (1) stability; (2) lack of odor ;(3) no causation of irritation to the skin; (4) no causation of sensitization of the human skin on exposure to sun-light; (5) oil compatibility; (6) protection against both the burning rays and the tanning rays of the sun; having heretofore been described.

Sun-screening compounds in general have been developed which afford satisfactory protection against the burning rays of the sun but which would permit the tanning rays to be transmitted. In the approximate range of from about 2,900 to 3,100 angstrom units are found the most detrimental burning wavelengths in the sun's rays. The effect of these wavelengths on the human skin is to produce a severe burning, reddening, blistering and edema which is characteristic of many burns. Obviously, this is not only *not* desirable from an esthetic point of view, but is a severe detriment to human health. In order, therefore, to overcome this effect of the burning rays of the sun, chemical compounds have been heretofore employed to screen out these burning rays. On the assumption and general acceptance by the public that tanning is a desirable phenomenon and is somewhat related to "good health," the public has been educated to accept the numerous products currently available to screen out the burning rays of the sun but to permit tanning to occur. Within the recent years it has become generally accepted that while tanning may have some beneficial effects especially in that it protects the skin from further burning where there is continued exposure to the sun, nevertheless, tanning in and of itself is associated with a general deterioration of the skin due to the effect of the actinic radiation thereon. While the great majority of people are not severely affected by tanning, there are a great number who are so sensitive to even the tanning rays of the sun that exposure to these wavelengths creates serious health hazards. Others have not quite accepted the notion that tanning is beautifying and would prefer to remain untanned. Consequently for those who must have protection against both burning and tanning rays of the sun, and for those who do not desire to be tanned, there has been a need for broad spectrum sun-screening compositions, which would give adequate protection to the skin, would be sufficiently stable under conditions of use to remain effective for several hours, which could be readily applied to the skin, which would be compatible with the various oily cosmetic compositions currently on the market, which would be aesthetically pleasing (for example, odorless) which would be non-irritating and non-sensitizing to the skin and which would not be readily removed such as by simple water-wash. The need for the latter characteristic is evident since it would leave one with a false sense of security if the material were readily removed as, for example, in bathing.

The term "non-sensitizing" is used herein to mean that the compounds of this invention will not induce or enhance or augment photosensitivity of the skin or exposure to ultraviolet light for a wavelength in the range of from about 2900 A. to about 3400 A.

In order, therefore, to achieve the ends of the present invention, it is necessary to provide a composition (1) which has an outstanding filtering action on those rays of the sun from about 2900 A. to about 3400 A.; which range encompasses the burning and tanning wavelengths present in sunlight, and (2) which is odorless, non-irritating and non-sensitizing to the skin.

It is further necessary to provide a composition having the foregoing properties which is either substantially oil-miscible or capable of forming a non-granular smooth suspension in oils [such as those used in standard cosmetic sun-screen compositions for application to the skin] so as to be compatible with the various cosmetic compositions currently available to the public.

It is further necessary to provide a composition having the foregoing properties, the ultraviolet radiation absorption properties of which will not be transformed as a result of a change in the pH of the environment of the compound.

One of the objects, therefore, of the present invention is to provide outstanding and useful compounds and compositions containing same which have excellent filtering action on the ultraviolet rays of solar light and particularly those wavelengths of from about 2,900 A. to about 3,400 A., as well as the ability to absorb the said rays even if the pH of the environment of the compound varies moderately.

It is still another object of the present invention to provide oily compositions, and particularly cosmetic compositions, which may be applied to the human skin to protect it against the burning and tanning rays of the sun and which are odorless, non-irritating and non-sensitizing to the skin;

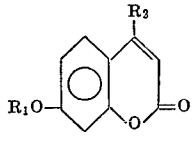
It is a still further object of the present invention to provide processes for preparing certain of the compounds with which the present invention is concerned and further, to provide processes for protecting the human skin against the burning and tanning rays of the sun.

Other objects will appear hereinafter as the description proceeds.

In accordance with the objects of the present invention, it has now been discovered that (1) a class of compounds hereinafter to be described has outstanding screening characteristics for the burning and tanning rays of the sun, and particularly those wavelengths in the ultraviolet region of from about 2,900 A. to about 3,400 A.; (2) that such compounds have unexpected superior light fastness and stability upon exposure to ultraviolet radiation; (3) that such compounds maintain their screening characteristics notwithstanding a change in the pH of the environment of said compounds; (4) that such compounds are compatible (that is, form stable suspension or are miscible) with oily compositions suitable for application to the human skin; and (5) that such compounds are odorless, non-irritating and non-sensitizing to human skin.

Known compositions containing 4-methyl-7-hydroxy-coumarin [see British Pat. 464,732 and Gregoire et al., Ann. Pharm. Franc., 9, 493–513 (1951)] have not been found to have all of the foregoing advantages. Such compounds do not have such stability that their screening characteristics are maintained in the event of a change in the pH of the environment of the compound; nor are they considered to be compatible with oily compositions suitable for application to the human skin, as are the compounds of this invention. By the same token, known compositions containing 4-methyl-7-methoxy coumarin or other 4-methyl-7-lower alkoxy coumarin or esculin (6,7-dihydroxy coumarin-6-glucoside) have not been found to have all of the advantageous properties of the compounds of this invention; particularly with regard to compatibility with oily compositions, and consistency of sun-screening charcateristics (in the event of a change in the pH of the environment of the compound).

The compounds found to be useful in the present invention and those which are employed in the compositions and processes of this invention have the following general formulae:



wherein R_1 is alkenyl, cycloalkenyl, alkadienyl, cycloalkadienyl, alkatrientyl, alkoxyalkadienyl, acyloxyalkadienyl, alkoxyalkenyl, cyclialkoxyalkenyl, aryl, alkaryl or aralkyl and R_2 is hydrogen or lower alkyl.

Suitable R_1 groups are:

(1) alkenyl of 3 to 15 carbon atoms;
(2) cycloalkenyl of 5 to 8 carbon atoms;
(3) alkadienyl of 5 to 20 carbon atoms;
(4) cycloalkadienyl of 6 to 10 atoms;
(5) aralkyl of 7 to 30 carbon atoms;
(6) alkaryl of 7 to 30 carbon atoms;
(7) aryl of 6 to 14 carbon atoms;
(8) alkatrienyl of 8 to 15 carbon atoms;
(9) alkoxyalkadienyl of 8 to 30 carbon atoms;
(10) acyloxyalkadienyl of 8 to 30 carbon atoms;
(11) alkoxyalkenyl of 8 to 30 carbon atoms;
(12) cyclialkoxyalkenyl of 8 to 30 carbon atoms.

Suitable R_2 groups are:

(1) hydrogen;
(2) methyl;
(3) ethyl;
(4) n-propyl;
(5) i-propyl;
(6) n-butyl;
(7) 2°-butyl;
(8) 3°-butyl.

Compounds of R_1 classes (2) and (4) and compounds of class (3) wherein R_2 is lower alkyl are novel compounds. The novel methyl-substituted compounds of class (3) are surprisingly oil soluble.

The general procedure for preparing the compounds found to be useful in this invention involves the reaction of a suitable halide with either 7-hydroxy coumarin (umbelliferone) or 7-hydroxy-4-lower alkyl coumarin. Suitable halide reactants are:

(1) alkenyl chlorides or bromides having 3 to 15 carbon atoms;
(2) cycloalkenyl chlorides or bromides having 3 to 15 carbon atoms;
(3) alkadienyl chlorides or bromides having from 5 to 20 carbon atoms;
(4) cycloalkadienyl chlorides or bromides having from 6 to 10 carbon atoms;
(5) aralkyl chlorides or bromides having from 7 to 30 carbon atoms;
(6) alkaryl chlorides and bromides having from 7 to 30 carbon atoms;
(7) aryl chlorides, bromides and iodides having from 6 to 14 carbon atoms;
(8) alkatrienyl chlorides of 8 to 15 carbon atoms;
(9) alkoxyalkadienyl chlorides of 8 to 30 carbon atoms;
(10) acyloxyalkadienyl chlorides of 8 to 30 carbon atoms;
(11) alkoxyalkenyl chlorides of 8 to 30 carbon atoms;
(12) cyclialkoxyalkenyl chlorides of 8 to 30 carbon atoms.

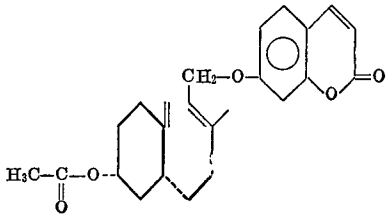
The condensation is carried out in the presence of a base, such as an alkali metal carbonate or bicarbonate, for example, potassium carbonate or sodium carbonate and in an organic solvent compatible with the reactants preferably an alkyl or alicyclic ketone such as acetone or cyclohexanone. Most preferably in view of convenience and economy the reaction is carried out at atmospheric pressure and at reflux conditions. Higher temperatures of reaction, and consequently higher pressures, will reduce the time of reaction. It is desirable, to add a catalyst such as potassium or sodium iodide in order to speed the reaction. At higher temperatures, the period of reaction varies from about 10 hours up to about 30 hours depending upon the particular halide used as the reactant and the yield of product desired. At the end of the period of reaction, the reaction product is isolated in the usual manner by means of crystallization or distillation where feasible.

Compounds of R_1 classes 8, 9, 10, 11 and 12 may also be produced using the procedures set forth in Caglioti et al., Helvetica Chim. Acta, vol. XLII, Fasciculus VII, 1959, No. 273–4, pages 2557–2564.

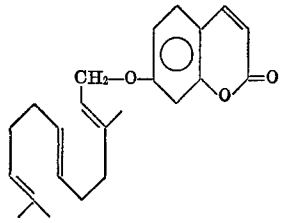
Among suitable ethers useful in this invention are:

7-allyloxy-4-methyl coumarin;
7-(3-methyl-2-buten-1-oxy)-4-methyl coumarin;
7-neryloxy-4-butyl coumarin;
7-geranyloxy-4-n-propyl coumarin;
7-geranyloxy-4-(1-n-butyl) coumarin;
7-benzoxy-4-methyl coumarin;
7-benzoxy-4-ethyl coumarin;
7-allyloxy coumarin;
7-(3-methyl cyclo hex-2-en) oxy-4-methyl coumarin;
7-geranyloxy-4-methyl coumarin;
7-neryloxy-4-methyl coumarin;
7-(3-methyl-2-buten-1-oxy) coumarin;
7-(3-methyl-2-buten-1-oxy)-4-n-propyl coumarin;
7-benzoxy coumarin;
7-(6-ethyl-cycloocta-2,4-dien) oxy-4-methy coumarin;
A mixture of 7-geranyloxy and 7-neryloxy coumarin;
A mixture of 7-geranyloxy and 7-neryloxy-4-methyl coumarins.

The compound of the structure:



Umbelliprenine having the structure:



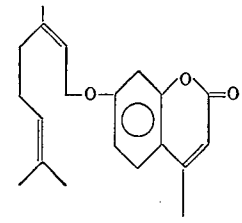
The range of usage of these compounds which are novel or which have been herein shown to be useful in oily sun-screening compositions is from about 1% up to about 10% (based on the weight of the final formula which is ready for use) with the preferred range being from about 1% up to about 6% by weight. Any oily carrier suitable for application to the human skin may be used, for example, lanolin, cetyl alcohol, wheat germ oil, sesame oil, polyethylene glycol stearate (wherein the polyethylene glycol moiety has a molecular weight of less than 400), other fatty acid esters of polyethylene glycol (wherein the polyethylene glycol moiety has a molecular weight of less than 400) and the like. After producing the formulation, application to the human skin may be made in any convenient and comfortable manner. An expedient application quantitiy is in the range of from 5 up to about 200 milligrams (of active ultraviolet absorption compound (coumarin ether)) per quare meter of skin, depending upon the environment of exposure and the nature of the skin being exposed. Thus, for example, exposure to high intensity ultraviolet radiation of highly sensitive skin would necessitate application concentrations at the upper part of the foregoing range.

The following examples serve only to illustrate the present invention. Percentages by weight are set forth therein unless otherwise indicated.

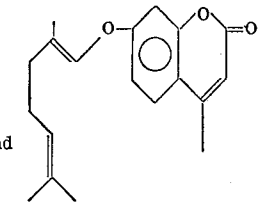
EXAMPLE I

Preparation of a mixture of 7-geranyloxy-4-methyl coumain and 7-neryloxy-4-methyl coumarin

To a flash fitted with a stirrer, a condenser and a thermometer was added 200 g. (1.14 moles) 4-methyl umbelliferone 280 g. (1.2 moles 77%) cold myrcene hydrochloride, consisting predominantly of geranyl and neryl chlorides produced by the process of U.S. Pat. 2,882,323, 680 g. of potassium carbonate, 10 g. of potassium iodide and 3.5 liters of acetone. The mixture was stirred and refluxed for 20 hours. The solution was filtered, and the supernatant liquid was retained for subsequent workup. Solid residue from this filtration was dissolved in a 2 N NaOH solution and this solution was then extracted with three 500 ml. volumes of CH_2Cl_2. The organic phases (the aforesaid supernatant liquid and the CH_2Cl_2 extracts) were combined and washed with two equal volumes of 2 N sodium hydroxide solution, followed by two equal volumes of water. 310 g. of crude reaction material was thereby produced. This crude product was steam distilled, to give 55 g. of steam volatiles. The residue after steam distillation was taken up in methylene chloride, and separated from the water layer. The organic layer was subjected to crystallization from petroleum ether to give 225 g. of a mixture of cis and trans isomers, 7-geranyloxy-4-methyl coumarin and 7-neryloxy-4-methyl coumarin. The following structures were confirmed by NMR data:



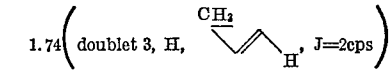
and



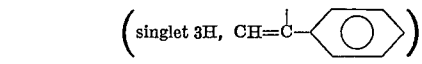
(7-neryloxy coumarin) (7-geranyloxy coumarin)

ϵ at 3220 A. =18100 (Extinction Coefficient)

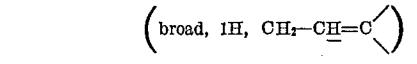
NMR data. ppm. 1.58, 1.63 (singlet, 3H each)

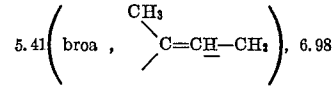


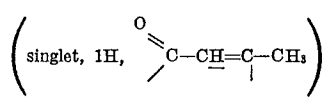
2.08 (broad, triplet, 4H, CH_2—CH_2), 2.39



4.57 (triplet, 2H HC≡C—O), 5.04







6.85 (2H, two aromatic protons), 7.54 (doublet, 1H, aromatic J=7)

EXAMPLE II

The product of Example I was incorporated into a neutral sun-screen cream as follows:

	Percent weight
The mixture of 7-neryloxy-4-methyl coumarin and 7-geranyloxy-4-methyl coumarin (Produced in Example I)	5.0
Polyethylene glycol 600-monostearate	5.0
Glyceryl monostearate	5.0
Lanolin, anhydrous	2.0
Cetyl alcohol	1.5
Stearic acid	9.5
Isopropyl myristate	2.0
Silicone—DC 200 (1000 centistokes, viscosity) A silicone manufactured by the Dow Corning Co. of Midland, Mich.	0.5
Propylene glycol	4.0
"Methyl 5-propyl-1-paraben" (A mixture of methyl and n-propyl para-hydroxy benzoates in a weight ratio of 1:5)	0.2
Distilled water	64.8
Trienthanolamine	0.5

The unexpected high miscibility of the product of Example I made it possible to formulate the above homogeneous cream. This cream was then used separately by five people in a bathing procedure, and thereafter the five persons were exposed to the summer afternoon sun for two hours. A similar group of five persons used a similar cream but devoid of the product of Example I, and these individuals were exposed similarly to the first group. All of the persons in the second group, after exposure, showed considerable reddening of the skin whereas none

of the persons in the first group had any visible evidence of sunburn. This demonstrates the sunscreening properties of the compound of Example I.

EXAMPLES III–V

In the following examples, Example I was carried out except that in place of myrcene hydrochloride, there were used the following halides in molar equivalent amounts:

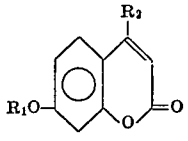
Ex.	Halide reactant	Reaction product	Ultraviolet data[ε at 3620A]
III	Allyl chloride	7-allyloxy-4-methyl coumarin	17,500
IV	Prenyl chloride	7(3-methyl-2-buten-1-oxy)-4-methyl coumarin.	17,600
V	Benzyl chloride	7-benzoxy-4-methyl coumarin	17,650

EXAMPLES VI–VIII

The compounds of Examples III–V were each added to a separate sample of the cream set forth in Example II. Substantially identical results were obtained using the compounds of Examples III–V, in place of the compound of Example I, except that the compounds of Examples III–V apparently formed suspensions rather than miscible systems with the oily sun-screen materials. Nevertheless, the products of Examples III–V were found to be compatible with the oily carrier.

What is claimed is:

1. A sun-screen composition comprising in an effective amount as a sun-screening agent a compound of the formula:



wherein R_2 is H or lower alkyl and wherein R_1 is selected from the group consisting of alkadienyl of five to 20 carbon atoms, cycloalkadienyl of six to 10 carbon atoms, and cycloalkenyl of five to eight carbon atoms and intimately admixed, therewith, a carrier acceptable for topical application to human skin.

2. A sun-screen composition comprising an effective sun-screening amount of a compound selected from group consisting of:

7-allyloxy-4-methyl coumarin
7(3-methyl-2-buten-1-oxy)-4-methyl coumarin
7-benzoxy-4-methyl coumarin
7-geranyloxy-4-methyl coumarin
7-neryloxy-4-methyl coumarin
7-allyloxy coumarin
7(3-methyl-2-buten-1-oxy) coumarin and
7-benzoxy coumarin

and, intimately admixed therewith, a carrier acceptable for topical application to human skin.

3. A sun-screen composition comprising an effective sun-screening amount of a mixture of 7-geranoxy-4-methyl coumarin and 7-neryloxy-4-methyl coumarin and, intimately admixed therewith, a carrier acceptable for topical application to human skin.

References Cited

Giese et al., J. Am. Pharm. Assoc., vol. 39, pp. 30–36 (1950).

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