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BENZOFURAN DERIVATIVES SUITABLE AS UV-ABSORBENTS

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U.S. Cl. 260—346.2 5 Claims

ABSTRACT OF THE DISCLOSURE

2-(2,4-dimethylphenyl)-benzofuran and 5-, 6-, or 7-methyl derivatives thereof suitable for absorbing UV-radiation of 290–320 mμ, and particularly useful as oil-soluble active ingredients for sun tan preparations and the like.

Applicants hereby claim the benefit of the filing date of German patent application M 69,570 of May 20, 1966.

This invention relates to novel derivatives of benzofuran, and more particularly to suntan preparations based on such derivatives.

Although there are many suntan preparations on the market, there are certain disadvantageous properties of the conventional active ingredients incorporated therein. Consequently, there is a particular need for active agents having better properties such as:

(1) More selective UV-absorption characteristics, permitting tanning, but preventing sunburn;

(2) Higher oil solubilities, permitting more of the agent to be incorporated in the carrier; and

(3) Better resistance to light and heat, resulting in minimum rancidity and longer shelf life.

An object of this invention, therefore, is to provide effective and novel compounds suitable as improved UV-absorbents.

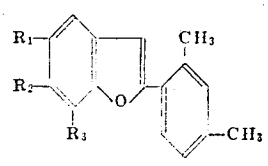
Another object is to provide processes and intermediates for the production of the novel compounds.

Still another object is to provide cosmetic preparations for the prevention of sunburn.

A still further object is to provide a process for absorbing and/or screening out UV-radiation by directing a source of UV-radiation on an object or mammal treated with a compound of this invention.

Upon further study of the specification and claims, other objects and advantages of the present invention will become apparent.

To attain the objects of this invention there are provided compounds of the following formula:



I

wherein: R_1, R_2, and R_3 represent hydrogen or methyl, with the provision that at least two of R_1, R_2, and R_3 represent hydrogen.

It has been discovered that compounds of Formula I are excellent UV-absorbers in the ultraviolet range of about 290–320 mμ, the wavelength range responsible for sunburns. For a clearer understanding of this effect, the absorption efficiency, measured in percent transmisison,

is tabulated below as a function of wavelength for the following compounds:

Ia—2-(2,4-dimethylphenyl)-benzofuran
Ib—2-(2,4-dimethylphenyl)-5-methyl-benzofuran
Ic—2-(2,4-dimethylphenyl)-6-methyl-benzofuran
Id—2-(2,4-dimethylphenyl)-7-methyl-benzofuran

In the following table, the data are based on solutions of 1 mg. of active agent in 100 ml. isopropanol and a layer thickness of 1 cm.

Wavelength in mμ	Percent transmission			
	Ia	Ib	Ic	Id
280	14.6	15.3	17.3	26.1
285	11.7	13.8	15.4	21.7
290	9.6	12.0	12.8	17.0
295	8.4	11.0	10.5	14.5
300	7.0	9.8	8.2	12.7
305	9.5	7.2	5.6	10.4
310	14.4	12.8	10.2	15.4
315	17.3	17.2	13.7	20.8
320	46.5	15.7	13.7	23.5
325	83.9	65.0	52.9	51.9
330	93.1	86.8	83.8	91.9

As can be seen from the above, the sunburn range between 290 and 320 mμ is substantially absorbed, while radiation above 330 mμ, which promotes tanning, is substantially unabsorbed.

Aside from selective UV-absorption, the compounds of Formula I are distinguished by an uncommonly high solubility in oils, especially paraffin oil. This solubility is unexpectedly much higher than the solubility of the unsubstituted 2-phenyl-benzofuran and methyl-substituted derivatives thereof, as evidenced by the following tabulated solubilities at 20° C.

Compound	Solubility in g./100 g. of paraffin oil	DAB 6 [Deutsches Arznei-Buch (German Drug Book)]
Ia	17.0	
Ib	7.0	
Ic	3.3	
Id	25.0	
2-phenyl-benzofuran	1.5	
2p-tolyl-5-methyl-benzofuran	0.5	

Still further advantages of the novel agents of this invention as compared to conventional UV-absorbers are: odorlessness, low toxicity, resistance to light and atmospheric conditions, and chemical stability. This latter advantage is particularly important inasmuch as the most common UV-absorbers are p-methoxycinnamic acid ethoxyethyl ester, p-dimethylaminobenzoic acid methyl and glycerine esters, all being subject to hydrolysis or saponification in time. The fact that the agents of this invention do not contain any ester groups eliminates the possibility of such decomposition reactions, thereby insuring a uniform efficaciousness.

The specific compounds of Formula I are all novel and unobvious albeit that German Patent 676,103 broadly describes an infinitely large class of compounds covering, inter alia, 2-aromatic-benzofurans.

For the production of suntan compositions, about 0.5 to 10, preferably 1 to 5 parts by weight of the novel active agents of this invention are incorporated with 100 parts by weight of a cosmetically acceptable carrier.

It is possible, for example, to produce, by the addition of salve or cream foundations and the like salves, ointments, pastes, and oily solids. By mixture with solvents, if desired, also with emulsifiers, there can be produced liquid and aerosol preparations.

Suitable cosmetically acceptable carriers are, for example, hydrocarbons, such as solid or liquid paraffin, ceresin, montan wax; vegetable or animal oils and fats,

such as olive oil, peanut oil, sesame oil, or almond oil; cocoa butter, beeswax, mineral wax or carnauba wax, wool fat, spermaceti; fatty acids and fatty acid esters, such as stearic, palmitic, and oleic acids, glycerin mono- or distearate, glycerin monooleate, isopropyl myristate, isopropyl stearate, butyl stearate; and ethyl, isopropyl, cetyl, stearyl, and palmityl alcohols. Moisturizing agents such as polyvalent alcohols, e.g. glycol, glycerine and sorbitol, are useful additives. As liquids, either oil-in-water or water-in-oil systems can be used, using commercially available emulsifiers of the non-ionic, cationic, anionic, or ampholytic types. To liquid systems it is also usual to add thickeners, such as methyl, ethyl, or carboxymethyl cellulose, polyacrylic acid, tragacanth, agar-agar, or gelatin. Furthermore, it is, of course, possible to add, if necessary or if desired, other additives, such as insect repellents, aerosol propellants, perfumes, preservatives, or physiologically compatible dyestuffs. Typical insect repellents are, for instance, the N,N-diethyl amides of caprylic and m-toluic acids, dimethyl phthalate, 2-ethyl-1,3-hexanediol, and butoxy polypropylene glycol. Suitable aerosol propellants comprise trichlorofluoromethane and dichlorodifluoromethane, furthermore nitrogen, carbon dioxide, propane, and butane.

To avoid sunburn, an effective amount of the active agent must be applied to the skin, this amount varying with the intensity and duration of the UV source, as well as with the complexion of the person's skin. In general, however, it is estimated that an application of about 10 to 100 mg. of active agent per 100 squart centimeters of skin surface should prevent sunburn for approximately 2–4 hours under direct midday summer light radiating in the northern temperate zone.

For general UV-screening use, the agents of this invention can also be incorporated with one or more other UV-absorbents, such as 2-phenylbenzimidazole-5-sulfonic acid sodium salt, 3,4-dimethylphenylglyoxylic acid sodium salt, 4-phenylbenzophenone, and isooctyl-4-phenylbenzophenone-2'-carboxylate.

The compounds of Formula I can be produced by standard reactions. For example, they can be obtained by reacting phenol (or o-, m-, or p-cresol) with chloroacetic acid to form phenoxyacetic acid (or o-, m-, or p-tolyloxyacetic acid); conversion of the thus-obtained product (for example, with thionyl chloride) into the corresponding acid halogenides (for example, phenoxyacetyl chloride); Friedel-Crafts reaction with m-xylene (for example, in the presence of aluminum chloride) to obtain 2,4-dimethyl-ω-phenoxyacetophenone (or 2,4-dimethyl-o-, -m-, or -p-tolyloxyacetophenone); and several hours of heating the same with polyphosphoric acid to temperatures between 100 and 170° C., preferably about 130° C., rearrangement taking place to 2-(2,4-dimethylphenyl)-benzofurans.

The reaction products can likewise be obtained by reacting salicylaldehyde (or 3-, 4-, or 5-methyl-salicylaldehyde) with lower alkyl esters of α-bromo-(2,4-dimethylphenyl)-acetic acid (preferably the methyl or ethyl ester thereof), subsequent saponification of the thus-obtained 2-(2,4-dimethylphenyl)-3-hydroxy - 2,3 - dihydrobenzofuran-2-carboxylic acid esters, as well as decarboxylation and dehydration.

Although the main field of application of the novel benzofuran derivatives is the cosmetical one, the compounds are also useful for technical and industrial uses. Chemical compositions and articles of manufacture can be provided which are resistant to UV radiation. In the technical field of application, the compounds of the invention are particularly advantageous for the inhibition of UV-initiated deterioration of organic polymers, both natural and synthetic, including polyvinyl chloride, polymethacrylates, cellulose acetate, polystyrene, polyvinyl acetate, and polyolefins such as polyethylene and polypropylene, and of common lacquers based on nitrocellulose, air- or oven-dried polyesters, epoxide resins, or polyol-diisocyanates.

Important novel intermediates in the process of manufacture of the novel benzofurans include:

α-(2-methyl-phenoxy)-2,4-dimethyl-acetophenone
α-(3-methyl-phenoxy)-2,4-dimethyl-acetophenone
α-(4-methylphenoxy)-2,4-dimethyl-acetophenone
3-hydroxy-2-(2,4-dimethylphenyl)-2,3-dihydrobenzofuran-2-carboxylic acid
3-hydroxy-2,(2,4-dimethylphenyl)-2,3-dihydro-5-methylbenzofuran-2-carboxylic acid
3-hydroxy-2-(2,4-dimethylphenyl)-2,3-dihydro-6-methylbenzofuran-2-carboxylic acid
3-hydroxy-2-(2,4-dimethylphenyl)-2,3-dihydro-7-methylbenzofuran-2-carboxylic acid
methyl and ethyl 3-hydroxy-2(2,4-dimethylphenyl)-2,3-dihydrobenzofuran-2-carboxylate
methyl and ethyl 3-hydroxy-2-(2,4-dimethylphenyl)-2,3-dihydro-5-methylbenzofuran-2-carboxylate
methyl and ethyl 3-hydroxy-2-(2,4-dimethylphenyl)-2,3-dihydro-6-methylbenzofuran-2-carboxylate
methyl and ethyl 3-hydroxy-2-(2,4-dimethylphenyl)-2,3-dihydro-7-methylbenzofuran-2-carboxylate

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative.

The numerical data in the following examples below are in parts by weight. In place of the active agent specifically set forth, 2-(2,4-dimethylphenyl)-benzofuran (Ia), it is possible to employ the above-mentioned compounds Ib, Ic or Id. Furthermore, if desired or if necessary, additives can be incorporated (for example, perfume, dyestuffs, preservatives, etc.).

EXAMPLE 1

Suntan oil:

2-(2,4-dimethylphenyl)-benzofuran	2
Paraffin oil	30
Refined peanut oil	68

EXAMPLE 2

Suntan oil with repellent effect:

2-(2,4-dimethylphenyl)-benzofuran	3
Liquid paraffin	20
Isopropyl myristate	57
Caprylic acid diethyl amide	5
m-Toluic acid diethyl amide	5
Dimethyl phthalate	10

EXAMPLE 3

Suntan cream:

2-(2,4-dimethylphenyl)-benzofuran	3
Sodium salt of cetyl-stearyl sulfate	2
Cetyl alcohol	10
Vaseline	20
Octadecyl alcohol	5
Spermaceti	1
Glycerin monostearate	1
Lanolin	1
Sorbitol solution, 70%	5
Water	47

EXAMPLE 4

Suntan lotion:

2-(2,4-dimethylphenyl)-benzofuran	3.0
Liquid paraffin	10.0
Polyoxyethylene ester of stearic acid	10.0
Isopropyl myristate	10.0
Sorbitol solution, 70%	5.0
Sodium laurylether sulfate	0.5
Water	61.5

EXAMPLE 5

Light-protective cream:

2-(2,4-dimethylphenyl)-benzofuran	3
Lanolin	67
Olive oil	10
Water	20

EXAMPLE 6

Aerosol:

Mixture according to Example 1	80
Mixture of trichlorofluoromethane and dichlorodifluoromethane (70:30) (propellant gas)	20

EXAMPLE 7

Light-protective cream:

2-(2,4-dimethylphenyl)-benzofuran	2
2 - phenyl - benzimidazole-5-sulfonic acid-triethanolamine salt, 50%	3
Commercial cream base (system: oil/water or water/oil)	95

EXAMPLE 8

Lipsticks: 100 g. commercially available lipstick mass is melted, and 2 g. of 2-(2,4-dimethylphenyl)-benzofuran are dissolved therein. The mass is poured into cooled lipstick molds, and the molded articles are removed after cooling.

The following examples demonstrate the production of the active agents of this invention:

EXAMPLE A

(a) 280 g. phenoxyacetyl chloride are dissolved in 830 ml. m-xylene; 155 g. aluminum chloride are added, and the mixture is heated for one hour under reflux conditions. After ice water is added to the reaction mixture, the resultant xylene phase is separated, and the resultant aqueous phase is extracted with benzene. The solvents are distilled from the combined solutions, and the residue is distilled at 205–210° C./12 mm. There is thus obtained 273 g. of α-phenoxy-2,4-dimethylacetophenone.

Analogously, the following compounds can be produced:

with o-tolyloxyacetyl chloride: α-(2-methylphenoxy)-2,4-dimethyl-acetophenone, B.P. 220–222° C./12 mm.;

with m-tolyloxyacetyl chloride: α-(3-methylphenoxy)-2,4-dimethyl-acetophenone, B.P. 219–221° C./12 mm.;

with p-tolyloxyacetyl chloride: α-(4-methylphenoxy)-2,4-dimethyl-acetophenone, B.P. 223–226° C./12 mm.

(b) 16.5 g. α-phenoxy-2,4-dimethyl-acetophenone and 165 g. polyphosphoric acid are heated to 132° C. for 2 hours with stirring. The reaction mixture is then poured over ice water and extracted with ether; the resultant ether solution is washed with a solution of sodium bicarbonate and dried over magnesium sulfate. After the solvent has been distilled off, the residue is distilled at 195–197° C./12 mm. There is thus obtained 10 g. of 2-(2,4-dimethylphenyl)-benzofuran which melts, after recrystallization from isopropanol, at 50–51° C.

Analogously, the following can be obtained:

2 - (2,4 - dimethylphenyl)-5-methyl-benzofuran, M.P. 67–69° C.; B.P. 210–215° C./12 mm.;

2 - (2,4 - dimethylphenyl)-6-methyl-benzofuran, M.P. 80–82° C. (from isopropanol);

2 - (2,4-dimethylphenyl)-7-methyl-benzofuran, B.P. 200–205° C./12 mm.

EXAMPLE B

(a) 25 g. salicylaldehyde and 50 g. α-bromo-(2,4-dimethylphenyl)-acetic acid ethyl ester are boiled for 4 hours in 100 ml. methylethyl ketone with the addition of 32 g. anhydrous potassium carbonate. The reaction mixture is cooled, diluted with ether, and filtered from the undissolved salt. The solvent is distilled from the filtrate, and the residue is degasified on a steam bath by a water jet aspirator. The remaining product, 3-hydroxy-2 - (2,4 - dimethylphenyl) - 2,3-dihydrobenzofuran-2-carboxylic acid ethyl ester, is mixed, without purification, with 60 ml. 32% sodium hydroxide solution, and heated on a steam bath until the contents of the flask are solid. Then, the mixture is vacuum-filtered; the residue is dissolved in water and acidified with concentrated hydrochloric acid. The oil which separates is taken up in chloroform, washed with water, dried, and the solvent is distilled off. There is thus obtained 30 g. 3-hydroxy-2-(2,4-dimethylphenyl) - 2,3 - dihydrobenzofuran - 2-carboxylic acid.

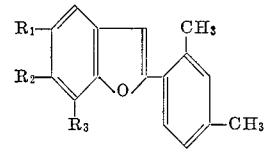
(b) 10 g. of the crude 3 - hydroxy - 2 - (2,4-dimethylphenyl)-2,3-dihydrobenzofuran-2-carboxylic acid are slurried up with 25 ml. water. Then, 10 ml. concentrated sulfuric acid is added, and the mixture is heated on a steam bath until the termination of CO_2 evolution. The thus-obtained crude product is distilled, thereby obtaining 8 g. of 2-(2,4-dimethylphenyl)-benzofuran having a boiling point of 195–197° C./12 mm. and a melting point of 50–51° C.

The preceding examples can be repeated with similar success by substituting the generically and specifically described reactants and operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention.

What is claimed is:

1. A compound of the formula:



wherein: R_1, R_2, and R_3 represent hydrogen or methyl, with the provision that at least two of R_1, R_2, and R_3 represent hydrogen.

2. A compound as defined by claim 1 wherein said compound is 2-(2,4-dimethylphenyl)-benzofuran.

3. A compound as defined by claim 1 wherein said compound is 2 - (2,4 - dimethylphenyl) - 5-methyl-benzofuran.

4. A compound as defined by claim 1 wherein said compound is 2 - (2,4 - dimethylphenyl) - 6-methyl-benzofuran.

5. A compound as defined by claim 1 wherein said compound is 2 - (2,4 - dimethylphenyl) - 7-methyl-benzofuran.

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