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Strobel

[11] **3,878,229**

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[54] **SUN-SCREENING COMPOUNDS III**

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[52] **U.S. Cl.** **260/404.5;** 260/472; 424/60

[51] **Int. Cl.** **C11c 3/00**

[58] **Field of Search** 260/404.5, 472

[56] **References Cited**

UNITED STATES PATENTS

3,536,723 10/1970 Ghelardoni et al. 260/472

Primary Examiner—Lorraine A. Weinberger
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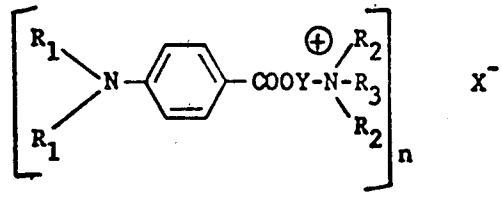
Attorney, Agent, or Firm—Walter C. Kehm; Samson B. Leavitt

[57] **ABSTRACT**

Sun-screening compounds, useful to protect the skin and hair against deleterious effects upon exposure to ultraviolet radiation, of the formula:



where R_1 and R_2 are independently straight or branched chain lower alkyl; Y is $C_2 - C_6$ alkylene; R_3 is alkyl of 8 to 18 carbon atoms; X is a cosmetically acceptable mono- or divalent anion; and *n* is 1 or 2 to provide an electrically neutral compound.

Sun-screening compositions containing such compounds and a cosmetically acceptable diluent or carrier, and methods of using such compositions, are also disclosed.

20 Claims, No Drawings

SUN-SCREENING COMPOUNDS III

The present invention relates to sun-screening compositions, methods of using the same and novel sun-screening compounds.

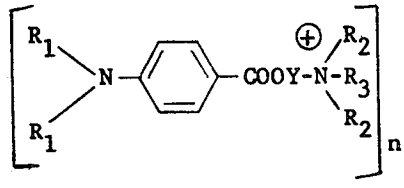
Ultraviolet radiation on the skin, such as from the sun, of a wavelength of 290 – 313 mμ is known to produce erythema, particularly in fair skinned subjects. On the other hand, ultraviolet radiation of from 315 – 320 mμ to 350 – 400 mμ promotes a tanning of the skin. To be effective, a sun-screening composition must at least remove substantially all of the burning rays, and in many instances a good portion of the tanning rays.

It is, therefore, an object of this invention to provide novel sun-screening compounds that are effective to prevent erythema.

It is a further object of the invention to provide new sun-screening compositions containing the sun-screening compounds of the invention.

These objects are provided by the provision of a sun-screening compound of formula (I):

(I)



where R_1 and R_2 are independently straight or branched chain lower alkyl; Y is C_2 – C_6 alkylene; R_3 is alkyl of 8 to 18 carbon atoms; X is a cosmetically acceptable mono- or divalent anion; and *n* is 1 or 2 to provide an electrically neutral compound. Preferably, X is halide, sulfate, phosphate, p-(lower alkyl) benzene sulfonate, benzoates, $R_4—COO^-$, $HOOC—R_5—COO^-$ or $^-OOC—R_5—COO^-$, where R_4 is alkyl of 1 to 18 carbon atoms and R_5 is alkylene of 1 to 18 carbon atoms. Such compounds show absorption of ultraviolet light in the range of 290 – 315 mμ and have good substantivity on the skin. The compounds of formula (I) are water soluble, but the degree of water solubility decreases as the number of carbon atoms in R_3 and/or R_4 and/or R_5 increase.

The term lower alkyl denotes a univalent saturated branched or straight hydrocarbon chain containing from 1 to 6 carbon atoms. Representative of such lower alkyl groups are thus methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.butyl, tert.butyl, pentyl, isopentyl, neopentyl, tert.pentyl, hexyl, and the like. The term alkylene of 2 to 6 carbon atoms denotes a divalent saturated straight or branched hydrocarbon obtained by removing a hydrogen atom from the lower alkyl defined above, excluding methyl.

The terms alkyl of 1 to 18 carbon atoms and alkyl of 8 to 18 carbon atoms denote a univalent saturatd branched or straight hydrocarbon chain containing

from 1 to 18 carbon atoms or 8 to 18 carbon atoms, repsectively. Representative of such alkyl groups are thus methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.butyl, tert.butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl and the like. The terms alkylene of 1 to 18 carbon atoms and alkylene of 8 to 18 carbon atoms denote a divalent saturated branched or straight hydrocarbon chain obtained by removing a hydrogen atom from the alkyl defined above.

The term halide denotes chloride, bromide, iodide and fluoride, preferably chloride or bromide.

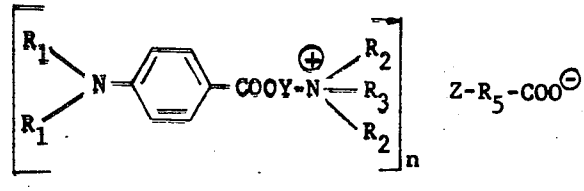
In a preferred embodiment of the invention, R_1 and R_2 are C_1–C_3 straight or branched chain alkyl.

It is further preferred to employ compounds in which R_3 is alkyl of 11 to 18 carbon atoms, because the more carbon atoms in R_3, the greater the substantivity of the compound of formula (I).

It is further preferred to employ compounds in which the anion, $R_4—COO^-$, is alkyl of 7 to 17 carbon atoms, e.g. as derived from a higher saturated aliphatic carboxylic acid, such as a C_8–C_{18} saturated aliphatic monocarboxylic acid, since such compounds will have reduced water-solubility and thus resist removal from the skin by water washing.

In another preferred embodiment of the invention, the anion, X, is derived from a saturated alphatic dicarboxylic acid ($HOOC—R_5—COOH$), and *n* is 1 or 2, preferably 2. The double salt of the dicarboxylic acid is preferred over the mono-salt, since the double salt shows improved affinity for the skin. Such compounds have the formula (Ia):

(Ia)



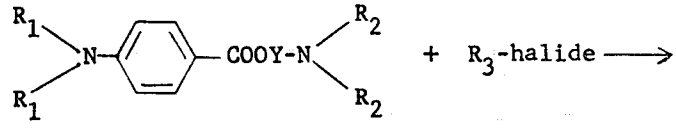
where R_1, R_2, R_3, and R_5 and *n* are as defined above, Z is —COOH or $—COO^-$, and *n* is 1 when Z is —COOH and *n* is 2 when Z is $—COO^-$. Preferably, the no carboxylic acid is one wherein R_5 is lower alkylene, and most preferably alkylene of 1 to 4 carbon atoms.

Compounds which are active as sun-screening agents are known and include such widely diverse compounds as dibenzylacetone, quinine sulfate and ethyl umbelliferone. Alkyl esters of p-dialkylaminobenzoic acid have also been proposed for use as sun-screening agents in U.S. Pat. Nos. 2,853,423; 3,403,207; and 3,479,428. In view of this highly empirical nature of the ability of a compound selectively to absorb ultraviolet radiation in the narrow range of 290 to 315 mμ, it was not expected that the compounds of formula (I) would be useful as sun-screening agents.

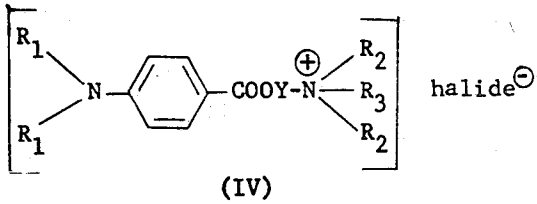
Mono-quaternary ammonium compounds useful as intermediates in the preparation of therapeutic agents have been proposed in U.S. Pat. No. 2,717,905. So far as we are aware, the sun-screening compounds of formula (I) are novel.

The quaternary salts of formula (I) where X is halide can be prepared by reacting at room temperature, with or without a solvent, approximately stoichiometric quantities of a dialkylaminoalkyl p-dialkylaminobenzoate (II) and an alkyl halide (III) to form the quaternary ammonium halide (IV), according to process (A) below:

(A)



(II) (III)



(IV)

where R_1, R_2 and R_3 are defined above, and "halide" is chloride, bromide, iodide or fluoride, preferably chloride or bromide.

Compounds of formula (I) where X is other than halide can be formed treating the quaternary ammonium halide (IV) with silver oxide to produce the mono-quaternary ammonium hydroxide. The excess silver oxide and precipitated silver halide is removed by filtration and the aqueous solution of mono-quaternary ammonium hydroxide then is reacted with an appropriate acid to introduce the desired anion, such as sulfonic acid, phosphoric acid, p-(lower alkyl) benzenesulfonic acid, benzoic acid or a mono- or dicarboxylic acid of the formula R_4—COOH or R_5—$(COOH)_2$.

Alternatively, the quaternary ammonium halide (IV) can be reacted with the desired acid in approximately stoichiometric quantities, in accordance with processes (B) or (C).

(B) R_4—COOH + (IV) → (I)

where R_4 is as defined above

(C) n(HOOC—R_5—COOH) + (IV) → (Ia)

where n is 1 or 2 and R_5 is as defined above.

The dialkylaminoalkyl p-dialkylaminobenzoate (II) used in process (A) is known, e.g. see U.S. Pat. No. 820,830, and can conveniently be made by alkylating an alkyl p-aminobenzoate with an alkyl halide in an organic solvent, and reacting the resulting alkyl p-dialkylaminobenzoate with a dialkylaminoalkanol.

For use in process (A), the dialkylaminoalkyl p-dialkylaminobenzoate may be:

dimethylaminoethyl p-dimethylaminobenzoate
diethylaminoethyl p-dipropylaminobenzoate
dimethylamioethyl p-dipentlyaminobenzoate
di-i-propylaminoethyl p-dihexylaminobenzoate
dihexylaminoethyl p-di-i-propylaminobenzoate
dimethylaminobutyl p-diethylaminobenzoate
dimethylaminohexyl p-diethylaminobenzoate
2-dimethylamino-2-methyl-ethyl p-dimethylaminobenzoate

The alkyl halide (III) used in process (A) is also known, and may be bromooctane, chlorooctane, iodooctane, fluorooctane, bromononane, chlorodecane, bromoundecane, bromododecane, chlorotetradecane, chlorohexadecane, bromooctadecane, chlorooctadecane and iodooctadecane.

The aliphatic monocarboxylic acid R_4—COOH used in reaction (B) may be acetic acid, n- or i-propanoic acid, n- or i-valeric acid, caprylic acid, octanoic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and nonadecanoic acid.

The aliphatic dicarboxylic acid R_5—$(COOH)_2$ used in reaction (C) may be malonic acid, succinic acid, adipic acid, 2,2'-dimethylglutaric acid, suberic acid, sebacic acid, dodecanedioic acid, tetradecanedioic acid, hexadecanedioic acid, and nonadecanedioic acid.

The following are representative sun-screening compounds of formula (I):

1. dimethyloctyl-(p-diethylaminobenzoyloxyethyl)-ammonium bromide
2. dimethyloctyl-(p-diethylaminobenzoyloxyethyl)-ammonium acetate
3. dihexyloctyl-(p-diethylaminobenzoyloxyethyl)-ammonium laurate
4. dimethyloctyl-(p-diethylaminobenzoyloxyethyl)-ammonium stearate
5. dimethyldecyl-(p-dihexylaminobenzoyloxyethyl)-ammonium chloride
6. dimethyldodecyl-(p-dimethylaminobenzoyloxyethyl)-ammonium 2-ethylhexanoate
7. dimethyloctadecyl-(p-dimethylaminobenzoyloxyethyl)-ammonium bromide
8. dimethyloctadecyl-(p-diemthylaminobenzoyloxyethyl)-ammonium 2-ethylhexanoate
9. dimethyldodecyl-(p-dimethylaminobenzoyloxybutyl)-ammonium caprylate
10. bis-[dimethyloctyl-(p-diethylaminobenzoyloxyethyl)-ammonium] malonate
11. bis-[dimethyldodecyl-(p-dimethylaminobenzoyloxybutyl)-ammonium] succinate
12. dimethyldodecyl-(p-diethylaminobenzoyloxyethyl)-ammonium succinate

The sun-screening agents of formula (I) are applied to the skin in the form of a sun-screen composition comprising the compound of formula (I) and a cosmetically acceptable diluent or carrier. The term "cosmetically acceptable diluent or carrier" denotes a non-toxic, non-irritating substance which when mixed with the compound of formula (I) makes the compound more suitable to be applied to the skin. The compositions can thus be solutions, oils, lotions, ointments, liquid or solid creams, aerosols and the like.

The sun-screening composition of the invention is formed by admixing dissolving or dispersing the sun-screening compound of formula (I) into the desired cosmetically acceptable diluent or carrier. Solutions are formed by dissolving the sun-screening compound in water or other solvent. Oils are prepared by using vegetable and/or mineral oils, such as sesame oil and/or white mineral oil as the cosmetically acceptable diluent or carrier. Creams may be prepared by adding lanolin and a suitable absorbent base to the vegetable and/or mineral oils. Oil-in-water emulsions may be employed as the vehicle to form lotions, but are not preferred since such compositions tend to wash off more easily than others.

An alcoholic lotion containing an alcohol, such as ethanol or isopropanol, and a film-forming substance as the cosmetically acceptable diluent or carrier is preferred, since this tends to provide more permanent protection even after exposure of the skin to water. Preferred film-forming agents for alcoholic lotions are cator oil, lauryl and oleyl alcohols, glycol and glyceryl oleates, mannitol and sorbitol oleate, laurate or ricinoleate, butyl stearate, ethyl oleate, laurate, or ricinoleate and methyl oleate, laurate or ricinoleate.

Perfumes, anti-oxidants, colorants, insect-repellants and the like may be included in the sun-screening composition, if desired.

The sun-screening composition of the invention contains an effective amount of the sun-screening compound of formula (I) to prevent erythema. In general, an amount of 0.01 to 10%, preferably 0.05 to 3%, by weight, of the total composition, of the sun-screening compound of formula (I) may be used. The composition is applied topically every few hours, as needed, in the same manner as conventional sun-screening compositions.

The compounds of the invention may also be used to protect blond and light-colored hair from the deleterious effects of ultraviolet radiation. In this case, the compounds of formula (I) are admixed with the cosmetically acceptable diluent or carrier to provide a composition containing from 0.05 to 10%, by weight, preferably 2 to 5%, by weight, of the compound of formula (I). The hair-protection compositions are applied to the hair in the same manner as a conventional hair lotion, hair cream or hair tonic, before exposure to ultraviolet radiation, and thereafter as desired. Cosmetically acceptable diluents or carriers used in such conventional hair preparations may be used in the hair-protection composition of the invention.

In the Examples, the following procedures were used:

TEST PROCEDURE ON SKIN

Reference solutions of the candidate compound in 50/50 ethanol-water solvent are prepared in concentrations of 2%, by weight, and below. Such solutions are applied to the skin and dried in air. Examination of the treated section of skin under UV light reveals a bluish-white color for untreated skin and brownish-black to black color fo treated skin.

A 2%, by weight, solution of the candidate compound in 50% ethanol-50% water is then rubbed into the skin, dried in air, and part of the air-dried surface is rinsed with water for 2 minutes. Examination of the rinsed and unrised sections of skin was then made in UV (black) light. The retention of the UV absorber on the skin is determined by observing the color of the treated and untreated sections under UV light and comparing the color to the reference solutions.

Tests for sunburn protection are carried out by applying a 2%, by weight, solution of the candidate compound in 50% ethanol-50% water to a small patch of skin, followed by exposure to sun for 2 hours. To be successful, a compound must prevent erythema after exposure for 2 hours to the sun at a latitude of New York City.

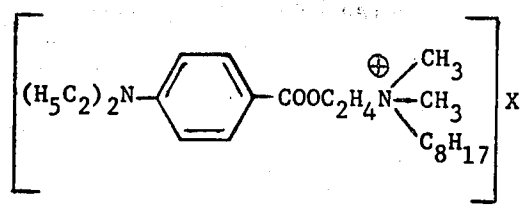
TEST PROCEDURE FOR HAIR

The substantivity of the candidate compound to hair is tested in the following manner. The candidate compound is dissolved in 100 mls. of water to provide a 0.1%, by weight, aqueous solution. 10 gms. of hair is immersed in the resulting aqueous solution, stirred for one-half hour, removed, rinsed and dried. The UV absorption of the aqueous solution into which the hair was immersed is measured both before and after the immersion of the hair in the solution, using the same technique described above. The % of the compound left after rinsing determines the amount of substantivity.

The following Examples illustrate the invention. In the Examples, all percentages and parts are by weight unless stated otherwise.

EXAMPLE 1

Preparation and application to the skin of:



where X = Br^- (Compound A) or CH_3COO^- (Compound B):

148g. ethyl p-aminobenzoate, 4.5g. ethyl iodide and 600 ml. ethanol were heated in an autoclave for 6 hours at 185°C. Then the solvent and excess ethyl iodide were evaporated at 120°C under atmospheric pressure, producing about 150g. ethyl p-diethylaminobenzoate.

70g. of this product, 2g. of sodium methoxide and 86g. dimethylaminoethanol were heated to 140°C for 24 hours while distilling off the ethanol that was liberated. The product was extracted with 200 ml. water and 100 ml. benzene, the water layer removed and the benzene evaporated to give about 80g. crude dimethylaminoethyl ester of p-dimethylaminobenzoic acid.

26.4g. of this compound was mixed with 21g. bromooctane and 100 ml. isopropanol. The mixture was refluxed for 24 hours, and the product evaporated to dryness on a steam bath. Compound (A) was recovered. An aqueous 0.1% solution of compound (A) was applied to skin and afforded protection against sunburn, but allowed tanning.

To a 1% aqueous solution of compound (A) was added 10% sodium acetate (based on the weight of the solution). The compound (B) precipitated, was filtered off and dried.

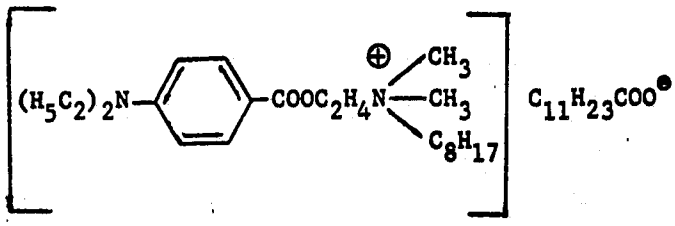
When 10g. hair was treated with 100 ml. aqueous solution containing 0.1% of compound (B), the hair was undue against indue deterioration on exposure to UV light. Substantivity was 75%, obtained by determining the K value of the solution before and after immersion of the hair. It also has similar substantivity and protective properties when applied to skin.

When the pH of the aqueous solution is adjusted to 8.5, compound (B) has higher substantivity on the skin and gives good protection against sunburn.

Maximum absorption of compounds (A) and (B) is at 313 mμ.

EXAMPLE 2

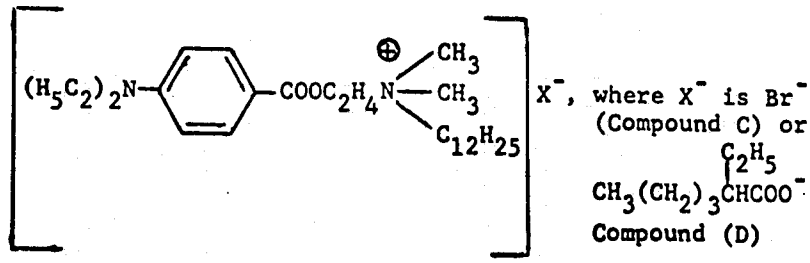
Preparation and application to the skin of the compound having the formula:



A 0.1% aqueous solution of the Compound (A) of Example 1 was adjusted to pH 7.0 with sodium laurate salt. Skin treated with this preparation was protected against sun-burn. Skin substantivity was excellent. Maximum absorption is at 313 mμ.

EXAMPLE 3

Preparation and application to the skin of the compound having the formula:



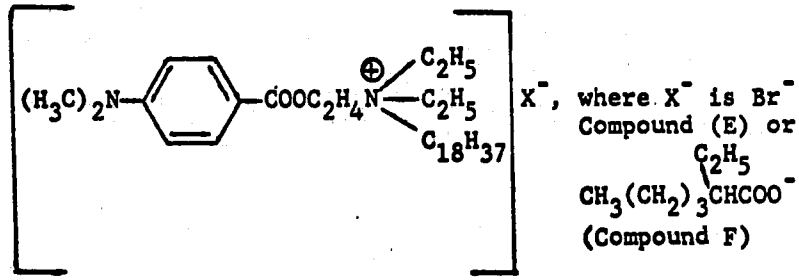
26.4 g. of dimethylaminoethyl ester of p-dimethylaminobenzoate was mixed with 28 g. bromododecane and 100 ml. iospropanol. The mixture was refluxed for 24 hours, and the product evaporated to dryness on a steam bath to give Compound (C).

An aqueous 0.1% solution of Compound (C) was adjusted to pH 7.0 with sodium 2-ethylhexoate to produce Compound (D).

Maximum absorption of Compound (D) was at 313 mμ. Skin substantivity of Compound (D) was excellent and there was a high degree of protection against sunburn.

EXAMPLE 4

Preparation and application to the skin of the product having the formula:



82.5 g. ethyl p-aminobenzoate, 100 ml. methanol and 65 g. dimethyl sulfate were mixed and gradually heated to 75°C. After 3 hours the charge was treated with 50 g. sodium carbonate to delta paper neutrality. It was then treated with 100 ml. benzene and 200 ml. water and the layers separated. The upper layer was evaporated free from benzene to give 80 g. ethyl p-dimethylaminobenzoate.

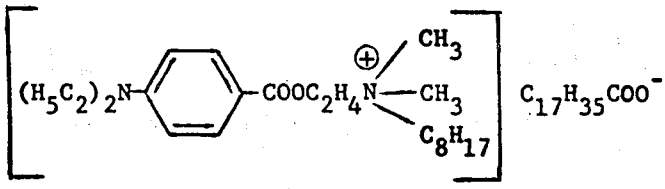
22.1 g. of this product, 0.50 g. sodium methoxide and 50 g. diethylaminoethanol were heated to 140°C. for 24 hours while distilling off the ethanol that was liberated. The product was extracted with 200 ml. water and 100 ml. benzene, the water layer removed and the benzene evaporated from the water layer to give about 80 g. crude diethylaminoethyl ester of p-dimethylaminobenzoic acid.

This product was then mixed with 32 g. bromooctadecane and 100 ml. isopropanol. The mixture was refluxed for 24 hours, and the product evaporated to dryness on a stream bath to give Compound (E).

An aqueous 0.1% solution of Compound (E) was adjusted to pH 7.0 with sodium 2-ethylhexoate to produce Compound (F), which was highly skin substantive and afforded excellent protection against sun-burning.

EXAMPLE 5

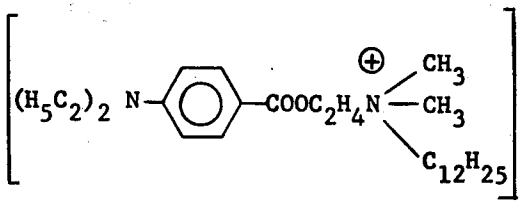
In the manner of Example 2, to a 1% aqueous solution of Compound (A) was added 10% sodium stearate to form:



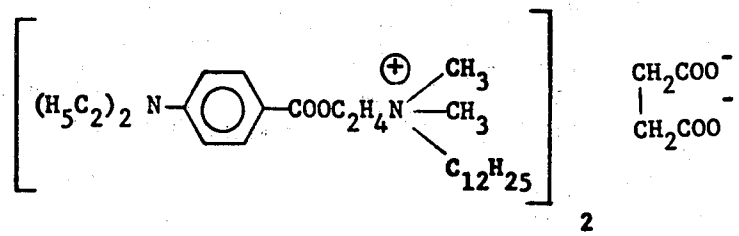
This compound had absorption at 313 mμ, affording excellent sun-burn protection on the skin against UV radiation, and a high degree of substantivity.

EXAMPLE 6

An aqueous 0.1% solution of



is treated with half the equimolar amount of the disodium salt of succinic acid to give



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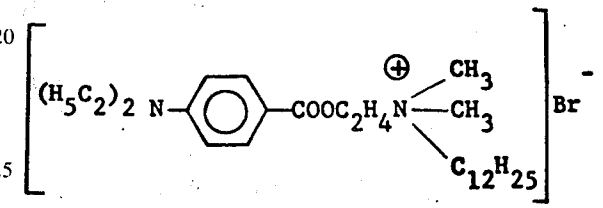
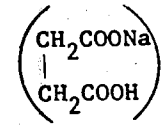
The precipitated product is filtered from the mixture and dried.

EXAMPLE 7

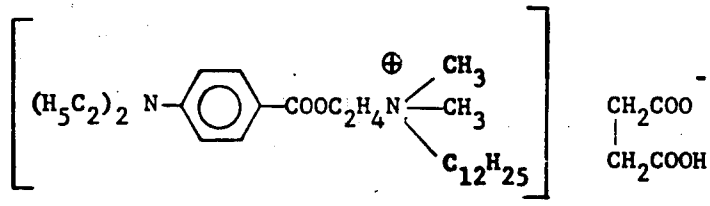
An aqueous 0.1% solution of



was treated with an equimolar amount of the monosodium salt of succinic acid



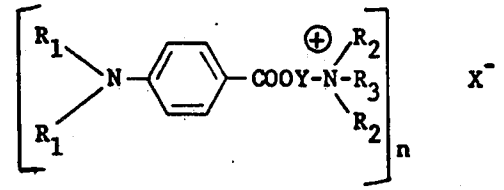
to give



The precipitated product is filtered from the mixture and dried.

I claim:

1. A compound of the formula:



wherein R_1 and R_2 are independently straight or branched chain lower alkyl; Y is $C_2 - C_6$ alkylene; R_3 is alkyl of 8 to 18 carbon atoms; X is an anion selected

from the group consisting of halide, sulfate, phosphate, p-(lower alkyl) benzene sulfonate, benzoate, R_4—COO^-, $HOOC—R_5—COO^-$ or $^-OOC—R_5COO^-$, where R_4 is alkyl of 1 to 18 carbon atoms and R_5 is alkylene of 1 to 18 carbon atoms; and n is 1 or 2 to provide an electrically neutral compound.

2. The compound according to claim 1, wherein R_1 and R_2 are straight or branched chain alkyl of 1 to 3 carbon atoms.

3. The compound according to claim 1, wherein R_3 is straight or branched chain alkyl of 11 to 18 carbon atoms.

4. The compound according to claim 1, wherein X is halide.

5. The compound according to claim 1, wherein X is $R_4—COO^-$ and n is 1.

6. The compound according to claim 5, wherein R_4 is alkyl or 7 to 17 carbon atoms.

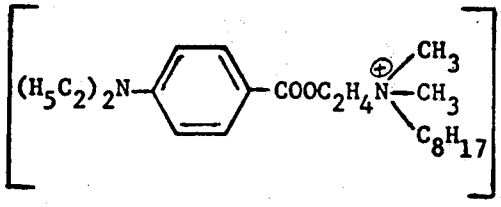
7. The compound according to claim 1, wherein X is $HOOC—R_5—COO^-$ and n is 1.

8. The compound according to claim 7, wherein R_5 is lower alkylene.

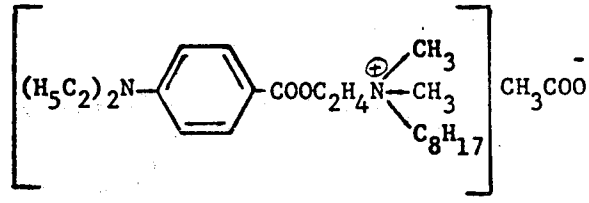
9. The compound according to claim 1, wherein X is $^-OOC—COO^-$ and n is 2.

10. The compound according to claim 9, wherein R_5 is lower alkylene.

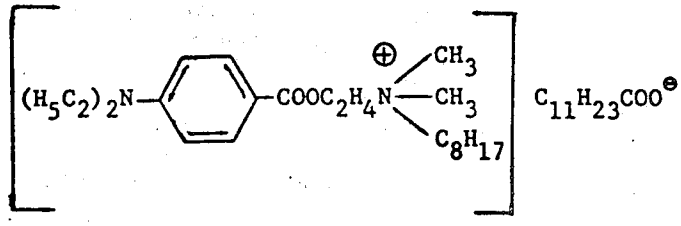
11. The compound according to claim 1, which is



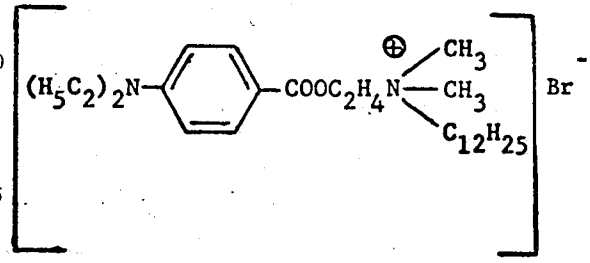
12. The compound according to claim 1, which is



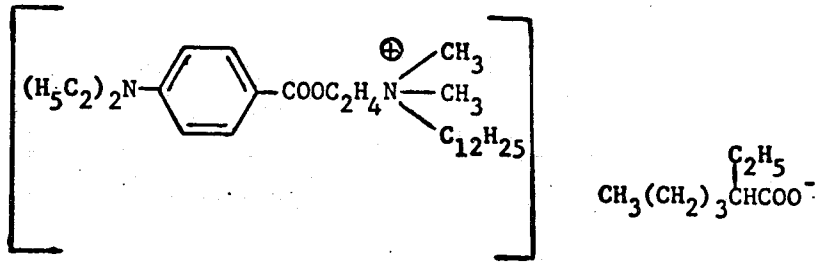
13. The compound according to claim 1, which is



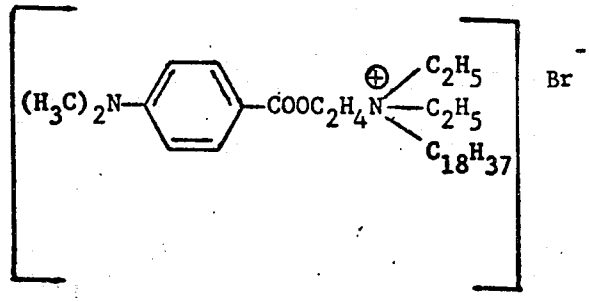
14. The compound according to claim 1, which is



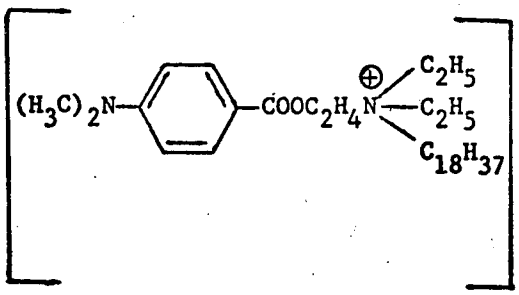
15. The compound according to claim 1, which is

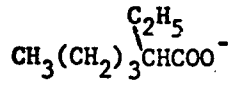


16. The compound according to claim 1, which is

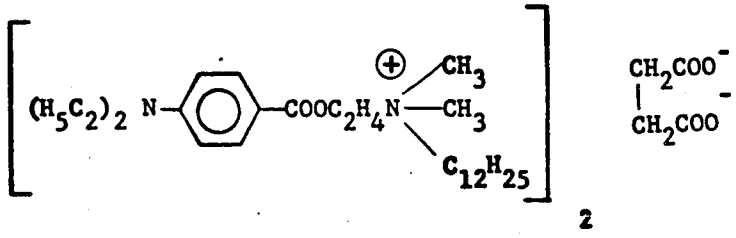


17. The compound according to claim 1, which is

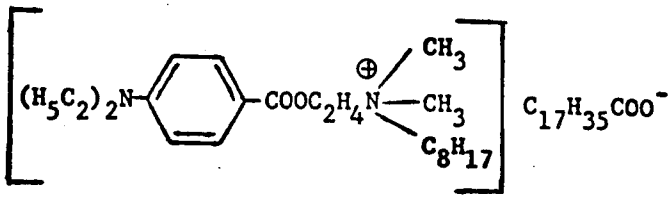




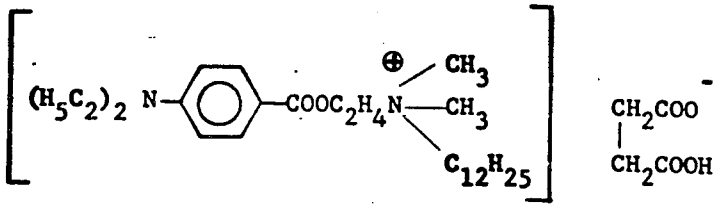
19. The compound according to claim 1, which is



18. The compound according to claim 1, which is



20. The compound according to claim 1, which is



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