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TRAITER LES DERMATOSES
(54) Title: L-CARNITINE SALT AND COSMETIC AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME FOR
TREATING DERMATOSES

(57) **Abrégé/Abstract:**

L-carnitine acid azelate and its use for producing cosmetic and pharmaceutical compositions suitable to be topically applied for the treatment of dermatoses, are disclosed.



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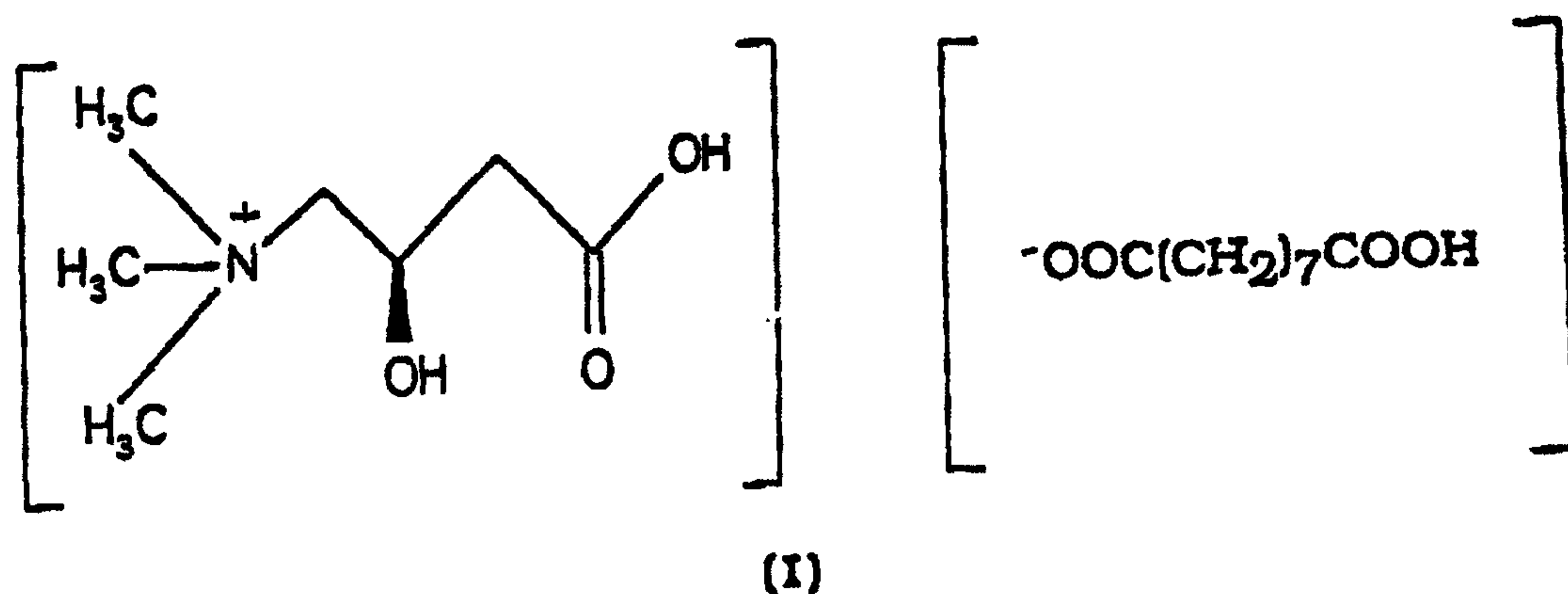
ABSTRACT

L-carnitine acid azelate and its use for producing cosmetic and pharmaceutical compositions suitable to be topically applied for the treatment of dermatoses, are disclosed.

L-CARNITINE SALT AND COSMETIC AND PHARMACEUTICAL
COMPOSITIONS CONTAINING SAME FOR TREATING DERMATOSES.

The present invention relates to a novel L-carnitine salt and the use thereof for producing cosmetic and pharmaceutical compositions which contain such salt, suitable to be topically applied for the treatment of dermatoses.

This novel L-carnitine salt is L-carnitine acid azelate of formula (I)



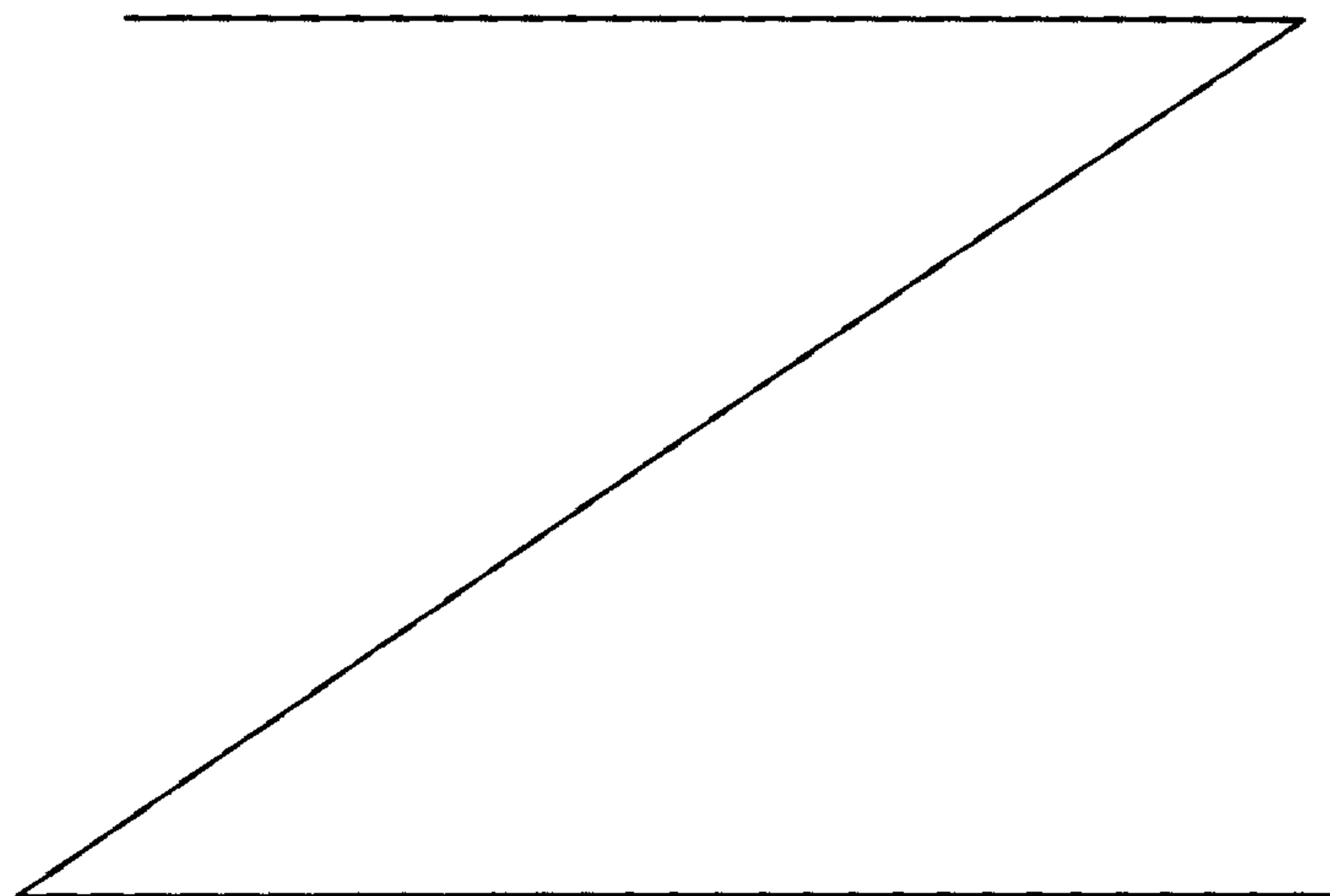
In another aspect, the invention provides a pharmaceutical composition suitable to be topically applied for treating dermatoses, which comprises the compound of formula (I) above as active ingredient, and a pharmacologically acceptable excipient therefor.

In a further aspect, the invention provides a cosmetic composition comprising the compound of formula (I) of above as cosmetically active ingredient, and a pharmaceutically acceptable excipient thereof.

L-carnitine acid azelate is a highly stable and non-hygrosopic salt.

1a

In the following example the preparation of L-carnitine acid azelate is described.



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EXAMPLE

Preparation of L-carnitine acid azelate (ST 1161)

L-carnitine inner salt (16,1 g ; 0,1 moles) was dissolved in 500 mL H₂O, Azelaic acid (18.82 g ; 0,1 moles), dissolved in 100 mL methanol was added to the L-carnitine solution.

The resulting solution was concentrated under vacuum at 40°C. The residue was taken up with acetone and the solid residue filtered off.

33 g of the title compound were obtained.

Melting Point : 59°C (DSC)

The compound is stable and non-hygroscopic.

Elementary analysis : C₁₆H₃₁NO₇

	C%	H%	N%
Calculated	55.00	8.94	4.00
Found	54.00	8.95	4.00

H₂O content 0,3%

pH = 4.09 (c = 0.5% ; H₂O)

25

$[\alpha]_D^{25} = -14,3$ (c=1%, MeOH)

D

HPLC

Column : SAX-SUPELCO (5 μm) ; 4,6 mm X 250 mm

Temperature : 30°C

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Eluant : KH_2PO_4 50mM/ CH_3CN (80/20); pH=7.0

Flow rate : 0.75 ml/min

Azelaic Acid : R_t =4.50 min 45.85%

L-carnitine : R_t =6.61 min 54.00%

NMR :

CD_3OD δ 4.5-4.4 (1H, m, CHOH) ; 3.3 (2H, m, CH_2N^+) ;

3.1 (9H, s, $(\text{CH}_3)_3\text{N}^+$) ;

2.5 (2H, dd, CH_2COO) ; 2.3-2.2 (4H, t, $\text{OOC}\underline{\text{CH}_2}(\text{CH}_3)_5\underline{\text{CH}_2}\text{OOH}$) ;

1.6 (4H, m, $\text{OOC}\underline{\text{CH}_2}\underline{\text{CH}_2}(\text{CH}_2)_3\underline{\text{CH}_2}\text{CH}_2\text{COOH}$) ;

1.3 (6H, s, $\text{OOC}(\text{CH}_2)_2\underline{\text{CH}_2}\underline{\text{CH}_2}\underline{\text{CH}_2}(\text{CH}_2)_2\text{COOH}$)

L-carnitine acid azelate is used as active ingredient for producing cosmetic and dermatologic pharmaceutical compositions suitable to be topically applied.

The dermatoses which are suitably treated with the compositions of the present invention are in particular ichthyosis, psoriasis and those dermatoses which are induced by a defective keratinization, such as dandruff, acne and palmar and plantar hyperkeratosis.

Ichthyosis is a dermatosis characterized by generalized dryness, harshness and scaling of the skin. It may occur as a hereditary disease present at birth, or as a metabolic disorder associated with hypothyroidism or with the intake of drugs (such as butyrophenols) inhibiting lipid synthesis, or as a

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paraneoplastic syndrome, manifestation of a tumor process involving internal organs.

Xeroderma, the mildest form of ichthyosis is neither congenital nor associated with systemic abnormalities. It usually occurs on the lower legs of middle-aged or older patients, most often in cold weather and in patients who bathe frequently. There may be mild to moderate itching and an associated dermatitis due to detergents or other irritants.

The inherited ichthyoses, all characterized by excessive accumulation of scale on the skin surface, are classified according to clinical, genetic, and histologic criteria.

Known treatments of any form of ichthyosis comprise topically applying to the skin hydrating emollients. Furthermore, salicylic acid or vitamin A-containing ointments have been widely used.

A keratolytic agent particularly effective in removing the scale in ichthyosis vulgaris, lamellar ichthyosis and sex-linked ichthyosis contains 6% salicylic acid in a gel composed of propylene glycol, ethyl alcohol, hydroxypropylene cellulose and water.

Further known drugs for the treatment of this disorder include: 50% propylene glycol in water, hydrophilic petrolatum and water (in equal parts), and cold cream

and an a-hydroxy acid (e.g.lactic and pyruvic acid) in various bases. In lamellar ichthyosis, 0.1% tretinoin (vitamin A acid ; retinoic acid) cream has been utilized. None of these treatments has been found satisfactorily effective.

Hyperkeratosis is a thickening of the stratum corneum of the skin.

The treatment of choice is the topical application of drugs containing urea, propylene glycol or salicylic acid. Also in this case, none of the known treatment has proved to be satisfactorily effective.

It has now been found that the compound of the present invention, when topically applied as solutions, lotions, cream or ointments containing from 0,01% to 20%, preferably from 1% to 15% and most preferably from 2 to 10% by weight of at least one of the foregoing compounds, are potently effective in achieving complete remission of ichthyotic conditions in humans and in healing psoriasis and those disorders brought about by an altered keratinization, such as dandruff, acne and palmar and plantar hyperkeratosis.

It has also been found that, if the solutions, creams or ointments of the invention are applied regularly on a daily basis, within about two to three weeks the

effected skin areas will return to normal conditions.

In order to prepare the compositions of this invention, L-carnitine acid azelate is preferably dissolved in water or ethanol initially. The solution thus prepared may be admixed in the conventional manner with commonly available ointment bases such as hydrophilic ointment (USP) or petrolatum (USP).

The water or ethanol used to dissolve the compounds according to this invention may range in concentration of from 1 to 30%, by volume, of the total composition. The compounds of this invention may also be formulated in a solution or lotion form.

For instance, an ester according to the invention is dissolved directly in a mixture of water, ethanol and propylene glycol (40:40:20 by weight).

Some examples of the formulation are herein below described:

Formulation 1:5% solution

5 grams of the salt were dissolved in 5 mL of water and the resulting solution admixed with 40 mL of ethanol and 20 mL of propylene glycol. Sufficient water was added to make 100 mL of formulation.

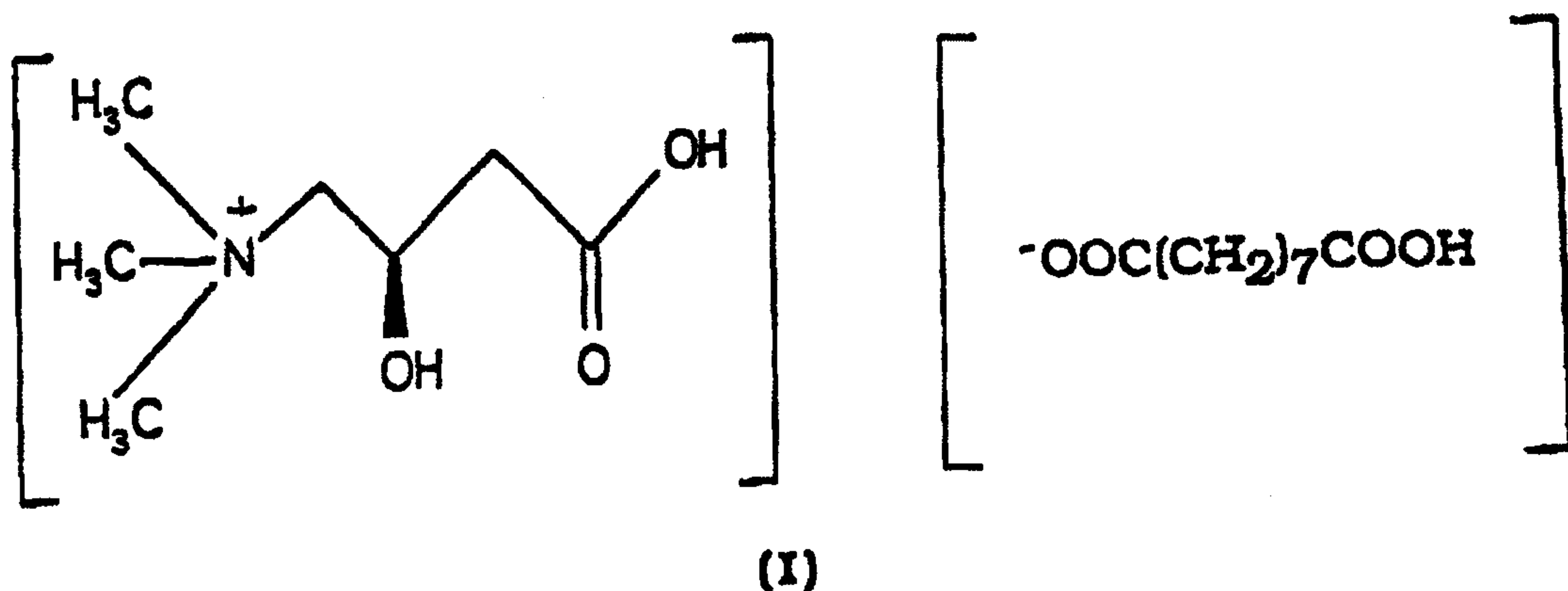
Formulation 2:5% ointment

5 grams of the salt were admixed with 95 grams of USP grade hydrophilic ointment, until an uniform

consistency resulted.

CLAIMS

1. L-carnitine acid azelate of formula (I)



2. A pharmaceutical composition suitable to be topically applied for treating dermatoses, which comprises the compound of formula (I) of claim 1 as active ingredient, and a pharmacologically acceptable excipient therefor.
3. The composition of claim 2 for treating ichthyosis and psoriasis.
4. The composition of claim 2 for treating dermatoses brought about by defective keratinization.
5. The composition of claim 4 for treating dandruff, acne and palmar and plantar hyperkeratosis.

6. The composition of anyone of the claims 2-5 in the form of solution, lotion, ointment or cream.

7. The composition of claim 6 which comprises from 0,01% to 20% by weight, of the salt of formula (I).

8. The composition of claim 6 which comprises from 1% to 15% by weight, of the salt of formula (I).

9. The composition of claim 6 which comprises from 2% to 10% by weight, of the salt of formula (I).

10. A cosmetic composition comprising the compound of formula (I) of claim 1 as cosmetically active ingredient, and a pharmaceutically acceptable excipient thereof.