

## Description

This invention relates to novel amide derivatives and dermatologic preparations containing the same. More particularly, it relates to dermatologic preparations capable of essentially improving the barrier functions of the horny layer, namely, maintaining normal barrier functions and restoring damaged barrier functions.

The horny layer is located on the outermost side of the skin to cover the whole body to thereby protect the body from external irritation and invasion of foreign substances and inhibit the evaporation of the moisture contained in the body.

When these barrier functions of the horny layer are weakened by some reasons, the skin frequently suffers from troubles such as inflammation or chapping.

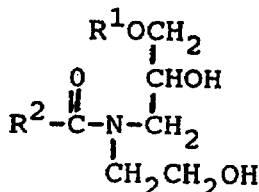
Furthermore, it is known that poverty or deficiency of essential fatty acids (for example, arachidonic acid or linoleic acid), which is caused by prolonged intake of foods free from essential fatty acids, would be accompanied by disorders in the barrier functions of the horny layer.

As the results of analyses on intercellular lipids, it has been found out that the intercellular lipids of the horny layer, in particular O-acylceramide, significantly contributes to the maintenance of the above-mentioned barrier functions of the horny layer.

It is believed, furthermore, that lipids secreted from sebaceous glands form a sebaceous membrane on the surface of the skin so as to partially make up for the barrier functions of the horny layer. Thus dermatologic preparations containing, for example, vaseline have been used in order to form a coating on the surface of the skin so as to make up for the barrier functions of the horny layer.

However known dermatologic preparations cannot essentially improve the barrier functions of the horny layer but merely form a tentative coating on the surface of the skin so as to make up for the barrier functions.

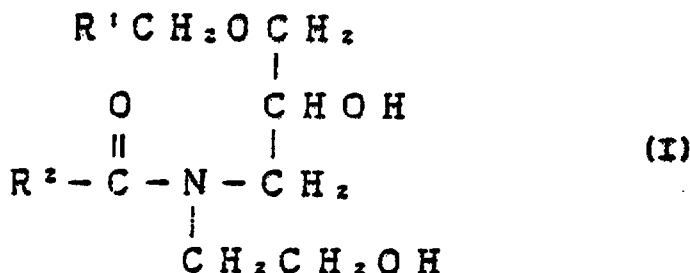
EP-A-0227994 suggests the use of amide derivatives of the formula



wherein  $R^1$  is a linear or branched, saturated or unsaturated hydrocarbon group having 10 to 26 carbon atoms and  $R^2$  is a linear or branched, saturated or unsaturated hydrocarbon group having 9 to 25 carbon atoms for improving the water retainability of keratin layers or essential prevention or cure of chappings in the skin.

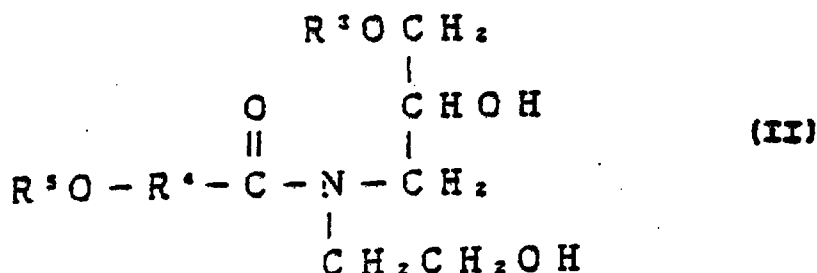
It is the object underlying the present invention to provide amide derivatives capable of maintaining the normal barrier functions of the horny layer and restoring damaged barrier functions and dermatologic preparations containing same which improve the barrier functions of the horny layer so as to suppress inflammation and chapping.

According to the present invention, this object is attained with an amide derivative represented by the following general formula (I):



wherein  $R^1$  and  $R^2$  represent each a straight-chain or branched, saturated or unsaturated hydrocarbon group provided that one of them carries 26 to 39 carbon atoms while the other carries 9 to 39 carbon atoms;

and with an amide derivative represented by the following general formula (II):



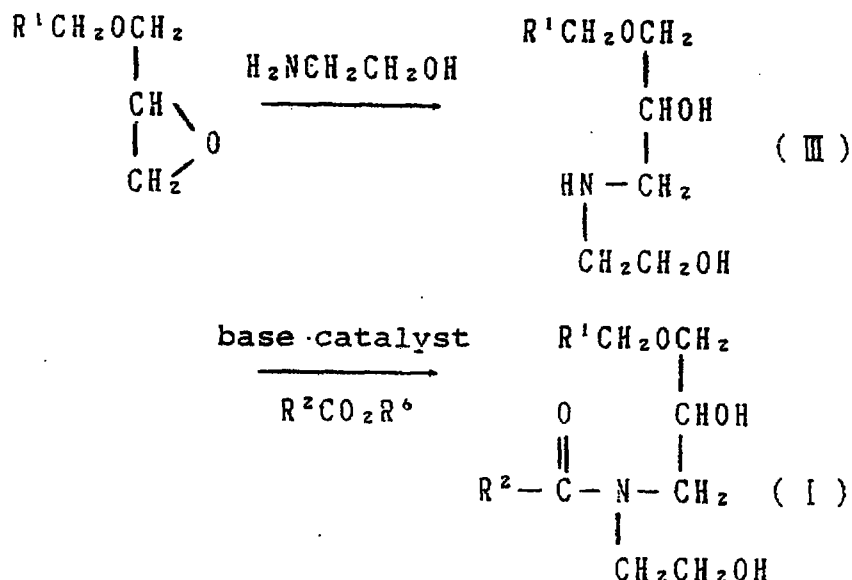
wherein  $\text{R}^3$  represents a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms;  $\text{R}^4$  represents a straight-chain or branched hydrocarbon group carrying 3 to 39 carbon atoms; and  $\text{R}^5$  represents a hydrogen atom, a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms or a straight-chain or branched, saturated or unsaturated acyl group carrying 10 to 40 carbon atoms.

Further, the present invention provides a dermatologic preparation containing an amide derivative of the above formula (I) or (II).

The dermatologic preparations of the present invention containing the amide derivatives of the present invention represented by the above general formula (I) or (II) are effective in essentially improving the barrier functions of the horny layer. When applied to the skin, they can suppress inflammation and chapping.

Firstly, the amide derivative of the present invention represented by the above-mentioned general formula (I) will be described.

The amide derivative of the present invention represented by the above-mentioned general formula (I) may be prepared in accordance with a known method described in, for example, Japanese Patent Laid-Open No. 216852/1988. That is, it may be obtained according to the following reaction scheme wherein a compound (III) prepared from glycidyl ether and ethanolamine is reacted with a fatty acid lower alkyl ester in the presence of a base catalyst while distilling off the lower alcohol thus formed:



(wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined above; and  $\text{R}^6$  represents an alkyl group carrying one to five carbon atoms).

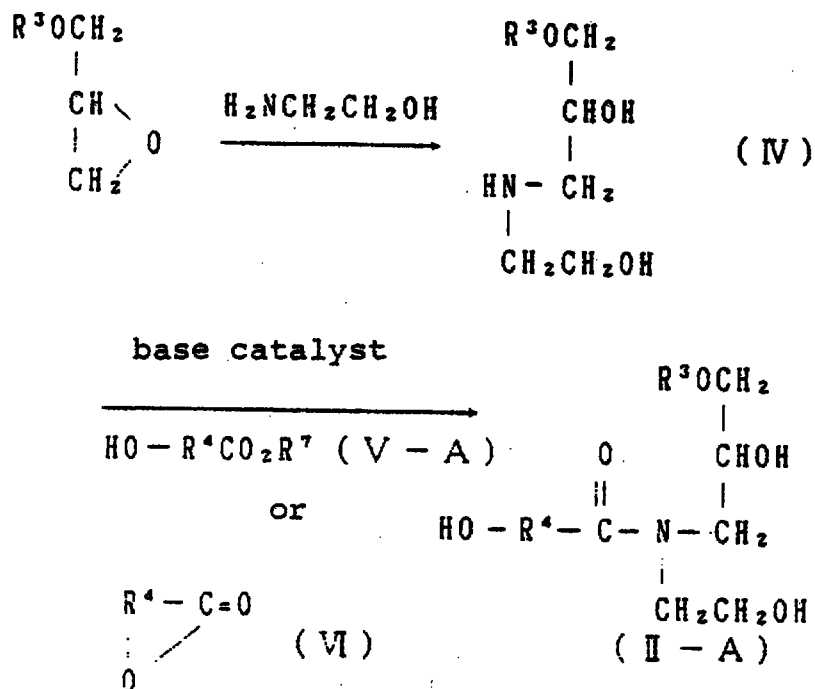
Next, the amide derivative of the present invention represented by the above-mentioned general formula (II) will be described.

The method for preparing the amide derivative of the present invention represented by the general formula (II) is not particularly restricted. Thus it may be prepared by, for example, the following methods (1)

to (3).

(1) Method for preparing an amide derivative (II-A) of the general formula (II) wherein  $R^5$  is a hydrogen atom:

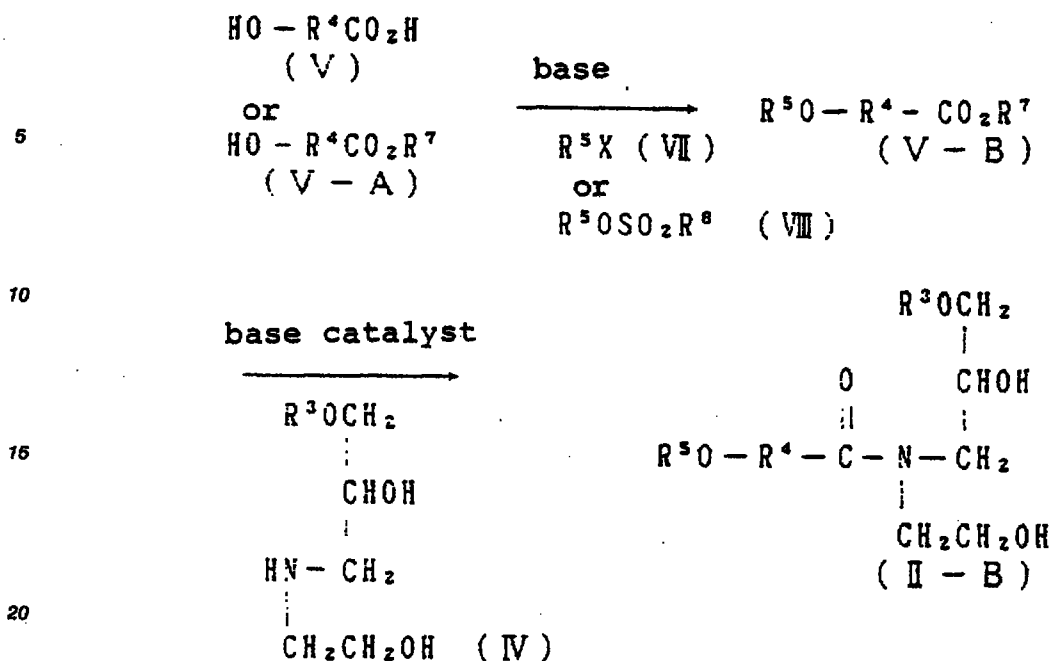
This derivative (II-A) may be prepared in accordance with a known method described in, for example, Japanese Patent Laid-Open No. 216852/1988. According to the following reaction scheme, an amine derivative (IV) prepared from glycidyl ether and ethanolamine is reacted with a hydroxy fatty acid lower alkyl ester (V-A) or a hydroxy fatty acid lactone (VI) in the presence of a base catalyst while distilling off the lower alcohol thus formed:



(wherein  $R^3$  and  $R^4$  are as defined above; and  $R^7$  represents an alkyl group carrying one to five carbon atoms).

(2) Method for preparing an amide derivative (II-B) of the general formula (II) wherein  $R^5$  is a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms:

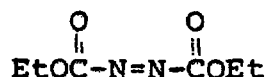
This derivative (II-B) may be prepared in accordance with the following reaction scheme wherein a hydroxy fatty acid (V) or a hydroxy fatty acid ester (V-A) is reacted with an alkyl halide (VII) or an alkyl sulfonate (VIII) in the presence of a base to give an etherified fatty acid ester (V-B), which is then reacted with an amide derivative (IV) obtained by the above method (1) in the presence of a base catalyst while distilling off the alcohol thus formed:



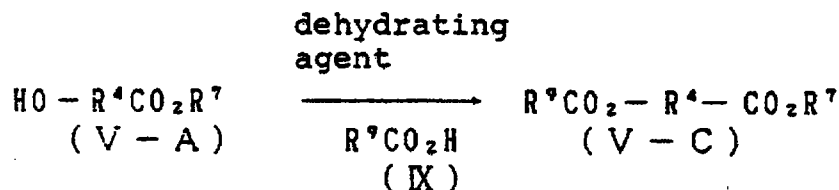
(wherein  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^7$  are as defined above;  $\text{R}^5$  represents a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms;  $\text{R}^8$  represents a methyl, phenyl or p-tolyl group; and X represents a chlorine, bromine or iodine atom).

(3) Method for preparing an amide derivative (II-C) of the general formula (II) wherein  $\text{R}^5$  is a straight-chain or branched, saturated or unsaturated acyl group carrying 10 to 40 carbon atoms:

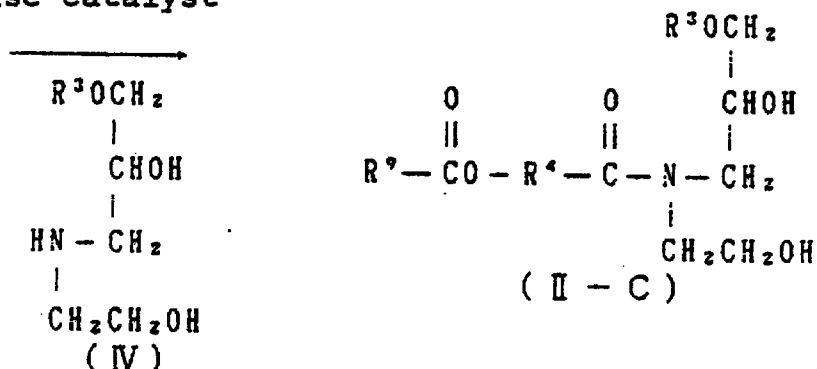
This derivative (II-C) may be prepared according to the following reaction scheme wherein a hydroxy fatty acid ester (V-A) is condensed with a fatty acid (IX) in the presence of an appropriate dehydrating agent [such as



and  $\text{P}(\text{C}_6\text{H}_5)_3$ ] to give an acylated fatty acid ester (V-C), which is then reacted with the amide derivative (IV) obtained by the above method (1) in the presence of a base catalyst while distilling off the alcohol thus formed:



base catalyst



(wherein  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^7$  are as defined above; and  $\text{R}^9$  represents a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 9 to 39 carbon atoms).

Next, the dermatologic preparation of the present invention containing the amide derivative (I) or (II) of the present invention represented by the above general formula (I) or (II) will be described.

The content of the amide derivative (I) or (II) of the present invention in the dermatologic preparation of the present invention is not particularly restricted. In the case of an emulsion type preparation, the amide derivative (I) or (II) may be preferably contained in an amount of 0.001 to 50% (by weight, the same will apply hereinafter) based on the whole preparation. In the case of an oily preparation containing a liquid hydrocarbon such as squalane as a base, the amide derivative (I) or (II) may be preferably contained in an amount of 0.01 to 50%.

The dermatologic preparations of the present invention may be prepared by blending a base commonly used for dermatologic preparations with the amide derivative (I) or (II) of the present invention. The dermatologic preparations may be broadly classified into medicinal dermatologic preparations and cosmetics depending on the applications thereof.

Examples of the medicinal dermatologic preparations include various ointments containing medicinal ingredients. These ointments may contain either an oily base or an O/W or W/O emulsion base. The oily base is not particularly restricted and examples thereof include vegetable oils, animal oils, synthetic oils, fatty acids and natural and synthetic glycerides. The medicinal ingredients are not particularly restricted and, for example, analgesics, antiinflammatory agents, antipruritic agents, bactericides, astringents, skin emollients and hormones may be used therefor, if required.

In using the dermatologic preparations of the present invention as the cosmetic, the essential ingredient, i.e., the amide derivative (I) or (II) of the present invention may be arbitrarily blended with, for example, oleaginous components, humectants, ultraviolet absorbers, alcohols, chelating agents, pH modifiers, preservatives, thickeners, colorants and perfumes commonly employed in the art.

The dermatologic preparations may be formulated into various skin cosmetics including W/O and O/W emulsions, cream, cosmetic milky lotion, cosmetic lotion, lipstick, foundation, skin cleanser, hair tonic, hair styling lotion, hair nourishment and hair growth stimulant.

#### [Function]

The function mechanism of the dermatologic preparations of the present invention containing the amide derivative (I) or (II) of the present invention represented by the above-mentioned general formula (I) or (II) has not been completely clarified in detail. It is assumed, however, that the application thereof to the skin as

the dermatologic preparation might serve to reinforce the intercellular lipid membrane of the horny layer so as to improve the barrier function of the horny layer.

To further illustrate the present invention, the following Examples will be given.

#### 5 Example 1

Synthesis of N-(2-hydroxy-3-hexadecyloxypropyl)-N-2-hydroxyethyltriacontanamide (Ia) [amide derivative of the general formula (I) wherein R<sup>1</sup> is C<sub>15</sub>H<sub>31</sub> and R<sup>2</sup> is C<sub>29</sub>H<sub>59</sub>]:

#### 10 (1) Synthesis of N-(2-hydroxy-3-hexadecyloxypropyl)ethanolamine (IIIa):

61.1 g (1.0 mol) of ethanolamine was introduced into a 200-ml four-necked flask equipped with a stirrer, a dropping funnel, a thermometer and a reflux condenser and heated to 60 to 70 °C under stirring. 24.3 g (0.082 mol) of hexadecyl glycidyl ether was added dropwise thereto over a period of 45 min. After the addition was completed, the resulting mixture was heated and stirred under the same conditions as those described above for additional 2 h. Then unreacted ethanolamine was distilled off under reduced pressure (79 to 81 °C/2.7kPa (20 Torr)). The residue was purified by silica gel flash column chromatography to thereby give 18.4 g of the compound (IIIa) at a yield of 63%.

The data of the <sup>1</sup>H-NMR of the obtained compound are as follows:

20 <sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.85(t, 3H), 1.23(bs, 28 H), 2.6~2.8(m, 4H), 3.1~3.9(m, 10H)

#### (2) Synthesis of the amide derivative (Ia):

25 5.39 g (15 mmol) of the compound (IIIa) obtained in the above item (1) and 0.042 g (0.75 mmol) of KOH were introduced into a 50-ml flask equipped with a stirrer, a dropping funnel, a thermometer and a distilling tube. While stirring the mixture by heating under reduced pressure (90 °C/2.7kPa (20 Torr)), 7.00 g (15 mmol) of methyl triacontanoate was added dropwise thereto over a period of 1.5 h. After the completion of the addition, the mixture was further stirred under the same conditions as those described above for additional 2 h. The crude product thus obtained was purified by silica gel flash column chromatography to thereby give 8.95 g the compound (Ia) at a yield of 75%. The melting point and IR and <sup>1</sup>H-NMR data of the obtained compound are as follows:

m.p.: 82.2~83.0 °C

IR: 3310, 2920, 2854, 1617, 1470, 1110, 1062, 720 cm<sup>-1</sup>

35 <sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.88(t, J=6.5Hz, 6H), 1.01~1.73(m, 82H), 2.31~2.45 (m, 2H), 3.08~4.28 (m, 13H)

#### Example 2

40 Synthesis of N-(2-hydroxy-3-dotriacontyloxypropyl)-N-2-hydroxyethyltriacontanamide (Ib) [amide derivative of the general formula (I) wherein R<sup>1</sup> is C<sub>31</sub>H<sub>63</sub> and R<sup>2</sup> is C<sub>29</sub>H<sub>59</sub>]:

The procedure of Example 1 (1) was repeated except that the hexadecyl glycidyl ether was replaced with dotriacontyl glycidyl ether to thereby give the compound (Ib) in the form of a colorless powder at a yield of 71%. The melting point and IR and <sup>1</sup>H-NMR data of the obtained compound are as follows:

m.p.: 88.2~88.9 °C

IR: 3316, 2920, 2854, 1617, 1467, 1107, 1059, 720 cm<sup>-1</sup>

<sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.88(t, J=6.6Hz, 6H), 0.99~1.72(m, 114H), 2.25~2.45(m, 2H), 2.95~4.28(m, 13H)

#### 50 Example 3

Synthesis of N-(2-hydroxy-3-dotriacontyloxypropyl)-N-2-hydroxyethylhexadecanamide (Ic) [amide derivative of the general formula (I) wherein R<sup>1</sup> is C<sub>31</sub>H<sub>63</sub> and R<sup>2</sup> is C<sub>15</sub>H<sub>31</sub>]:

55 The procedure of Example 1 was repeated except that the hexadecyl glycidyl ether used in Example 1 (1) was replaced with dotriacontyl glycidyl ether and the methyl triacontanoate used in Example 1 (2) was replaced with methyl hexadecanoate to thereby give the compound (Ic) in the form of a colorless powder at

a yield of 80%. The melting point and IR and <sup>1</sup>H-NMR data of the obtained product are as follows:

m.p.: 62.6~64.0 °C

IR: 3304, 2920, 2854, 1617, 1467, 1056, 720cm<sup>-1</sup>

<sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.88(t, J=6.6Hz, 6H), 0.98~1.71 (m, 86H), 2.25~2.48 (m, 2H), 3.24~4.25 (m, 13H)

#### Example 4

The dermatologic preparations of the present invention comprising 10% of each of the amide derivatives of the present invention listed in Table 1 and 90% of squalane were prepared. Then the transepidermal water loss and percutaneous absorption of each dermatologic preparation were evaluated in the following manner. For comparison, a comparative dermatologic preparation comprising squalane alone was also evaluated. Table 1 summarizes the results.

#### (Test method)

Wistar male rats were fed with a feed free from essential fatty acids. Then each dermatologic preparation was applied to the shaven dorsal skin of the rat showing essential amino acid deficiency once a day for three weeks. On the next day of the completion of the application for three weeks, the following items were examined.

Each lot involved three rats.

#### (1) Transepidermal water loss

The dorsal skin of the rat was washed with water at 37 °C and the animal was allowed to stand in a room at 20 °C under a humidity of 45% for 1 h. Then the transepidermal water loss was measured with an evaporimeter. A larger water loss means lower barrier functions of the horny layer and more serious chapping.

When the normal barrier functions are maintained, this value is smaller than 10. On the other hand, an essential fatty acid deficient rat having damaged barrier functions shows a value exceeding 35. Each value is expressed in "mean ± standard deviation".

#### (2) Percutaneous absorption

The dorsal skin of the rat was washed with water at 37 °C. Next, said skin was cut and inserted into a percutaneous absorption chamber with the epidermal side thereof directed upward. A lower receiver of the chamber was filled with a phosphate buffer equilibrated salt solution while a container on the epidermal side thereof was charged with 1 ml of a solvent containing 37 KBq of <sup>14</sup>C-salicylic acid. After 2 h, the amount of the <sup>14</sup>C-salicylic acid penetrating into the lower receiver was determined. When the normal barrier functions are maintained, the <sup>14</sup>C-salicylic acid scarcely penetrates after 2 h. This value increases as the barrier functions are more seriously damaged. Each value is expressed in "mean ± standard deviation".

Table 1

|                      | Amide derivative       | Transepidermal water loss | Percutaneous absorption |
|----------------------|------------------------|---------------------------|-------------------------|
| Product of Invention | compound of Ex. 1 (Ia) | 29.2 ± 6.8                | 546 ± 260               |
|                      | compound of Ex. 2 (Ib) | 20.8 ± 7.2                | 778 ± 265               |
|                      | compound of Ex. 3 (Ic) | 18.6 ± 4.8                | 546 ± 320               |
| Comparison           | squalane alone         | 35.8 ± 9.6                | 1220 ± 240              |

#### Example 5

By using each of the amide derivatives of the present invention, the dermatologic preparations of the present invention of the compositions as specified in Table 2 (emulsion cosmetic) were prepared. The effect

of each product of improving skin chapping was evaluated in the following manner. For comparison, a dermatologic preparation free from any amide derivative of the present invention (comparative product) was evaluated in the same manner. Table 3 summarizes the results.

#### 5 (Test method)

Ten female subjects aged 20 to 40 years, who suffered from chapping in cheeks in winter, were employed. Different dermatologic preparations were applied on the right and left cheeks of the subjects once a day for three weeks. On the next day of the completion of the application for three weeks, the following items were examined.

##### (1) Transepidermal water loss

The face of each subject was washed with water at 37°C and then she was allowed to stand in a room at 20°C under a humidity of 45% for 1 h. Then the transepidermal water loss was measured with an evaporimeter. A larger water loss means lower barrier functions of the horny layer and more serious chapping. When this value exceeds 40, serious chapping is observed. When it is smaller than 10, on the other hand, scarcely any chapping is observed. Each value is expressed in "mean  $\pm$  standard deviation".

##### 20 (2) Skin chapping score

Skin chapping was observed with the naked eye and evaluated based on the following criteria. Each score is expressed in "mean  $\pm$  standard deviation".

25

| score | Evaluation of chapping              |
|-------|-------------------------------------|
| 0     | no chapping observed.               |
| 1     | slight chapping observed.           |
| 2     | chapping observed.                  |
| 3     | somewhat serious chapping observed. |
| 4     | serious chapping observed.          |

30

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Table 2

(% by weight)

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|                                           | Invention products | Comparative product |
|-------------------------------------------|--------------------|---------------------|
| methyl-branched isostearyl glyceryl ether | 2.0                | 2.0                 |
| 2-octyldodecyl myristate                  | 10.0               | 10.0                |
| vaseline                                  | 3.0                | 3.0                 |
| squalane                                  | 5.0                | 5.0                 |
| tocopherol acetate                        | 0.5                | 0.5                 |
| amide derivative<br>(refer to Table 3)    | 1.0                | -                   |
| water                                     | the balance        | the balance         |

Table 3

|                     | Amide derivative       | Transepidermal water loss | Skin chapping score |
|---------------------|------------------------|---------------------------|---------------------|
| Invention product   | compound of Ex. 1 (Ia) | 24.3 ± 5.3                | 1.5 ± 0.3           |
|                     | compound of Ex. 2 (Ib) | 19.8 ± 6.4                | 1.3 ± 0.4           |
|                     | compound of Ex. 3 (Ic) | 17.6 ± 4.8                | 0.9 ± 0.3           |
| Comparative product | -                      | 28.6 ± 9.8                | 2.4 ± 0.7           |

## Example 6

Synthesis of N-(2-hydroxy-3-hexadecyloxypropyl)-N-  
2-hydroxyethyl-12-hydroxyoctadecanamide (II-Aa)  
[amide derivative of the general formula (II) wherein

OH  
 $R^3$  is  $C_{16}H_{33}$  and  $R^5O-R^4$  is  $C_6H_{13}\overset{|}{\underset{OH}{CH}}(CH_2)_{10}]$

## (1) Synthesis of N-(2-hydroxy-3-hexadecyloxypropyl)ethanolamine (IVa):

61.1 g (1.0 mol) of ethanolamine was introduced into a 200-ml four-necked flask equipped with a stirrer, a dropping funnel, a thermometer and a reflux condenser and heated to 60 to 70 °C under stirring. 24.3 g (0.082 mol) of hexadecyl glycidyl ether was added dropwise thereto over a period of 45 min. After the completion of the addition, the resulting mixture was stirred by heating under the same conditions as those described above for additional 2 h. Then unreacted ethanolamine was distilled off under reduced pressure (79 to 81 °C/2.7kPa(20 Torr)). The residue was purified by silica gel flash column chromatography to thereby give 18.4 g of the compound (IVa) at a yield of 63%. The <sup>1</sup>H-NMR data of the obtained compound are as follows:

<sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.85 (t, 3H), 1.23(bs, 28H), 2.6~2.8 (m, 4H), 3.1~3.9 (m, 10H)

## (2) Synthesis of amide derivative (II-Aa):

17.3 g (48 mmol) of the compound (IVa) obtained in the above item (1) and 0.14 g (2.5 mmol) of KOH were introduced into a 100-ml flask equipped with a stirrer, a dropping funnel, a thermometer and a distilling tube. While stirring the mixture by heating under reduced pressure (80 °C/2.7kPa(20 Torr)), 15.1 g (48 mmol) of methyl 12-hydroxyoctadecanoate was added dropwise thereto over a period of 1 h. After the completion of the addition, the mixture was further stirred under the same conditions as those described above for an additional 1 h. The crude product thus obtained was purified by silica gel flash column chromatography to thereby give 23.0 g of the compound (II-Aa) at a yield of 74%. The melting point and IR and <sup>1</sup>H-NMR data of the obtained compound are as follows:

m.p.: 70.8~71.3 °C

IR: 3352, 2926, 2854, 1617, 1473, 1122, 1077 cm<sup>-1</sup>

<sup>1</sup>H-NMR (δ, CDCl<sub>3</sub>):

0.88 (t, J=6.3Hz, 6H), 1.12~1.82 (m, 56H), 2.24~2.51 (m, 2H), 3.23~4.30 (m, 15H)

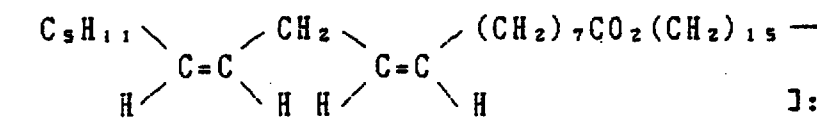


<sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.80~0.95(m, 6H), 0.95~1.70(m, 72H), 1.95~2.12 (m, 4H), 2.39(t, J=7.7Hz, 2H), 2.77(bt, J=5.7Hz, 2H), 3.39 (t, J=6.6Hz, 4H), 3.23~4.23(m, 13H), 5.24~5.44(m, 4H)

## 5 Example 9

Synthesis of N-(2-hydroxy-3-hexadecyloxypropyl)-N-  
2-hydroxyethyl-16-(9Z,12Z-octadecadienoyloxy)-  
hexadecanamide (II-Ca) [amide derivative of the  
general formula (II) wherein R<sup>3</sup> is C<sub>16</sub>H<sub>33</sub> and R<sup>5</sup>O-R<sup>4</sup> is



### (1) Synthesis of methyl 16-(9Z,12Z-octadecadienoyloxy)hexadecanoate (V-Ca):

4.30 g (15 mmol) of methyl 16-hydroxyhexadecanoate, 8.41 g (13 mmol) of linoleic acid, 7.87 g (30 mmol) of triphenylphosphine and 100 ml of tetrahydrofuran were fed into a 300-ml flask equipped with a stirrer, a dropping funnel and a thermometer and 5.22 g (30 mmol) of diethyl azodicarboxylate was added dropwise thereto at room temperature under stirring over a period of 1 h. After the completion of the addition, the mixture was further stirred at room temperature for 4 h. After distilling off the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography to thereby give 6.76 g of the compound (V-Ca) at a yield of 82%.

### (2) Synthesis of amide derivative (II-Ca):

2.74 g (5 mmol) of the compound (V-Ca) obtained in the above item (1), 1.80 g (5 mmol) of the amine (IVa) obtained in Example 1 (1) and 0.028 g (0.25 mmol) of potassium tert-butoxide were fed into a 50-ml flask equipped with a stirrer, a dropping funnel, a thermometer and a distilling tube. Then the mixture was stirred by heating under reduced pressure (80°C/2.7kPa (20 Torr)) for 30 min. The crude product thus obtained was purified by silica gel column chromatography and gel chromatography to thereby give 1.65 g of the compound (II-Ca) at a yield of 38%. The melting point and IR, <sup>1</sup>H-NMR and MS data of the obtained compound are as follows:

m.p.: 58.2~58.9°C

IR: 3304, 2920, 2856, 1734, 1612, 1464, 1440, 1216, 1166, 1108, 756, 720cm<sup>-1</sup>

<sup>1</sup>H-NMR(δ, CDCl<sub>3</sub>):

0.80~1.00(m, 6H), 1.00~1.73(m, 60H), 1.95~2.16 (m, 4H), 2.28(t, J=7.5Hz, 2H), 2.39(bt, J=7.7Hz, 2H), 2.77(bt, J=5.9Hz, 2H), 3.23~4.25(m, 13H), 4.05 (t, J=6.6Hz, 2H), 5.26~5.47 (m, 4H)

MS (FAB, POS):

877(M+1), 859, 634, 586, 360

(FAB, NEG):

875(M-1), 873, 831, 613, 534, 359, 305, 279

## Example 10

The dermatologic preparations of the present invention comprising 10% of each of the amide derivatives of the present invention listed in Table 4 and 90% of squalane were prepared. Then the transepidermal water loss and percutaneous absorption of each of the dermatologic preparations were evaluated in the same manner as those described in Example 4. For comparison, a comparative der-

matologic preparation comprising squalane alone was also evaluated. Table 4 summarizes the results.

Table 4

|                      | Amide derivative          | Transepidermal water loss | Percutaneous absorption |
|----------------------|---------------------------|---------------------------|-------------------------|
| Product of Invention | compound of Ex. 6 (II-Aa) | 26.7 $\pm$ 7.3            | 124 $\pm$ 36.2          |
|                      | compound of Ex. 7 (II-Ab) | 28.0 $\pm$ 8.4            | 516 $\pm$ 172           |
|                      | compound of Ex. 8 (II-Ba) | 12.4 $\pm$ 3.2            | 779 $\pm$ 76.6          |
|                      | compound of Ex. 9 (II-Ca) | 14.2 $\pm$ 4.2            | 340 $\pm$ 122           |
| Comparison           | squalane alone            | 35.8 $\pm$ 9.6            | 1220 $\pm$ 240          |

## Example 11

By using each of the amide derivatives of the present invention, the dermatologic preparations of the present invention of the composition as specified in Table 5 (emulsion cosmetic) were prepared. The effect of each product of improving skin chapping was evaluated in the same manner as the one described in Example 5. For comparison, a dermatologic preparation free from any amide derivative of the present invention (comparative product) was evaluated in the same manner. Table 5 summarizes the results.

Table 5

(% by weight)

|                                           | Invention products | Comparative product |
|-------------------------------------------|--------------------|---------------------|
| methyl-branched isostearyl glyceryl ether | 2.0                | 2.0                 |
| 2-octyldodecyl myristate                  | 10.0               | 10.0                |
| vaseline                                  | 3.0                | 3.0                 |
| squalane                                  | 5.0                | 5.0                 |
| tocopherol acetate                        | 0.5                | 0.5                 |
| amide derivative<br>(refer to Table 6)    | 1.0                | -                   |
| water                                     | the balance        | the balance         |

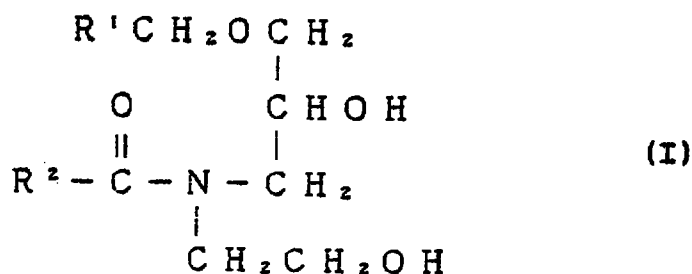
Table 6

|         | Amide derivative          | Transepidermal water loss | Skin chapping score |
|---------|---------------------------|---------------------------|---------------------|
| 5<br>10 | Invention product         |                           |                     |
|         | compound of Ex. 6 (II-Aa) | 25.4 ± 7.8                | 1.3 ± 0.3           |
|         | compound of Ex. 7 (II-Ab) | 22.8 ± 6.3                | 1.2 ± 0.4           |
|         | compound of Ex. 8 (II-Ba) | 12.1 ± 4.2                | 0.8 ± 0.3           |
|         | compound of Ex. 9 (II-Ca) | 12.3 ± 4.3                | 0.9 ± 0.3           |
|         | Comparative product       | -                         | 28.6 ± 9.8          |
|         |                           |                           | 2.4 ± 0.7           |

## Claims

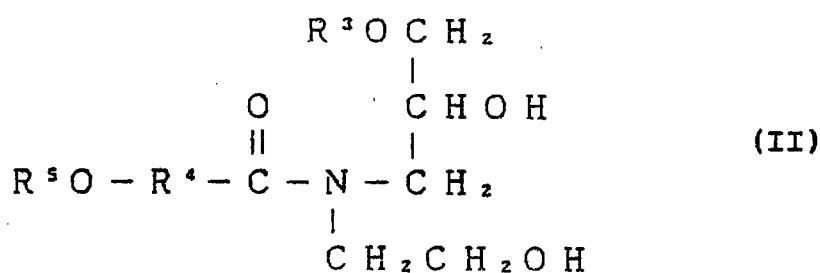
Claims for the following Contracting States : AT, CH, DE, FR, GB, LI, NL

1. An amide derivative represented by the following general formula (I):



wherein  $R^1$  and  $R^2$  represent each a straight-chain or branched, saturated or unsaturated hydrocarbon group provided that one of them carries 26 to 39 carbon atoms while the other carries 9 to 39 carbon atom).

2. An amide derivative represented by the following general formula (II):



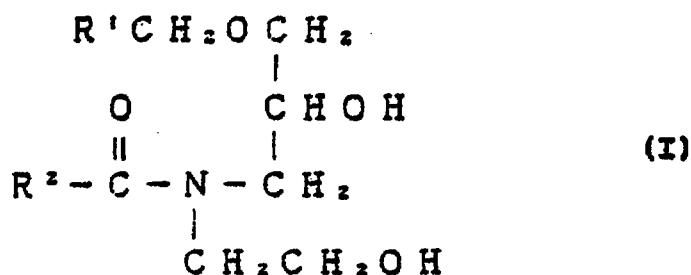
wherein  $R^3$  represents a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms;  $R^4$  represents a straight-chain or branched hydrocarbon group carrying 3 to 39 carbon atoms; and  $R^5$  represents a hydrogen atom, a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms or a straight-chain or branched, saturated or unsaturated acyl group carrying 10 to 40 carbon atoms.

3. A dermatologic preparation containing an amide derivative as claimed in claim 1 or 2.

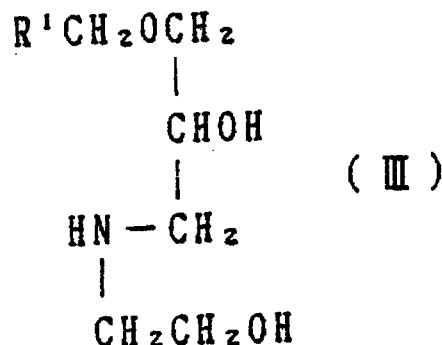


Claims for the following Contracting State : ES

1. A process for preparing an amide derivative represented by the following general formula (I):

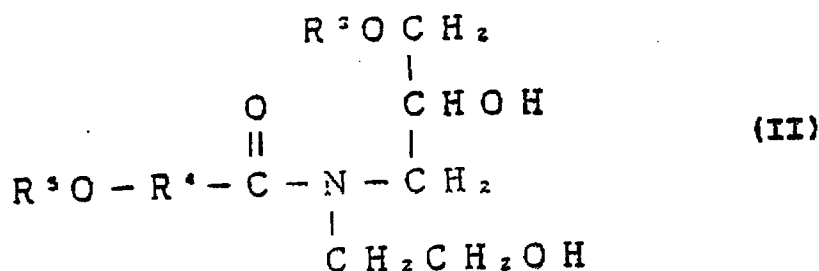


wherein  $R^1$  and  $R^2$  represent each a straight-chain or branched, saturated or unsaturated hydrocarbon group provided that one of them carries 26 to 39 carbon atoms while the other carries 9 to 39 carbon atoms, which comprises reacting a compound of the formula (III)



wherein  $R^1$  is as defined above, with a fatty acid lower alkyl ester of formula  $R^2CO_2R^6$ , wherein  $R^2$  is as defined above and  $R^6$  is a  $C_{1-5}$  alkyl group, in the presence of a base catalyst.

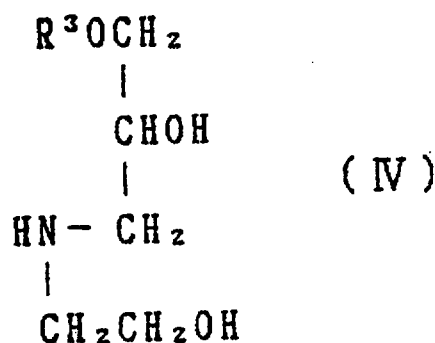
2. A process for preparing an amide derivative represented by the following general formula (II):



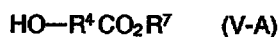
wherein  $R^3$  represents a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms;  $R^4$  represents a straight-chain or branched hydrocarbon group carrying 3 to 39 carbon atoms; and  $R^5$  represents a hydrogen atom, a straight-chain or branched, saturated or unsaturated hydrocarbon group carrying 10 to 40 carbon atoms or a straight-chain or branched, saturated or unsaturated acyl group carrying 10 to 40 carbon atoms, which comprises



(a) reacting an amine derivative of the formula (IV)

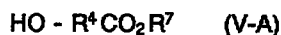


wherein  $R^3$  is as defined above, with a hydroxy fatty acid lower alkyl ester of the formula (V-A) or a hydroxy fatty acid lactone of the formula (VI)



wherein  $R^3$  and  $R^4$  are as defined above and  $R^7$  is a  $C_{1-5}$  - alkyl group, in the presence of a base catalyst; or

(b) reacting a hydroxy fatty acid of the formula (V) or a hydroxy fatty acid ester of the formula (V-A)

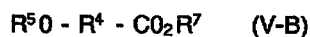


wherein  $R^4$  is as defined above and  $R^7$  is a  $C_{1-5}$  - alkyl group, with an alkyl halide of the formula (VII) or an alkyl sulfonate of the formula (VIII)

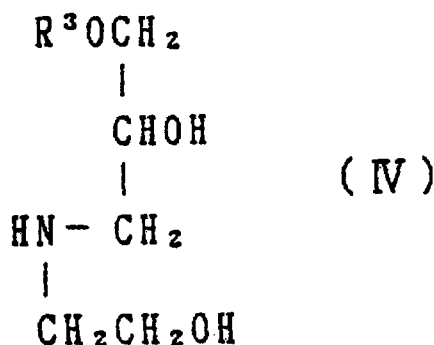


wherein  $R^5$  is a straight chain or branched saturated or unsaturated  $C_{10-40}$  - hydrocarbon group;  $R^8$  is methyl, phenyl or p-tolyl; and X is Cl, Br or I;

in the presence of a base, to obtain an etherified fatty acid ester of formula (V-B)



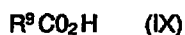
wherein  $R^4$ ,  $R^5$  and  $R^7$  are as defined above; and further reacting with an amide derivative of formula (IV)



wherein  $R^3$  is as defined above, in the presence of a base catalyst, or  
(c) condensing a hydroxy fatty acid ester of formula (V-A)



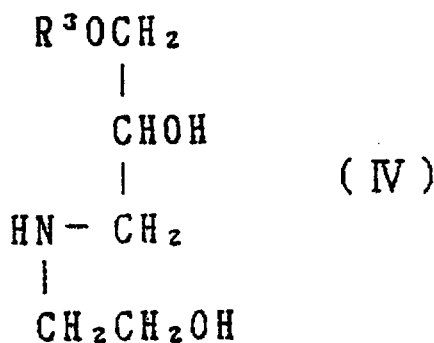
wherein  $R^4$  and  $R^7$  are as defined above,  
with a fatty acid of formula (IX)



wherein  $R^9$  is a straight chain or branched, saturated or unsaturated  $C_8-33$  - hydrocarbon group,  
in the presence of a dehydrating agent to give an acylated fatty acid ester of formula (V-C)



wherein  $R^4$ ,  $R^7$  and  $R^9$  are as defined above,  
which is then reacted in the presence of a base catalyst with an amide derivative of formula (IV)

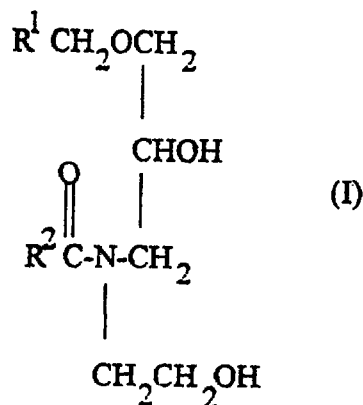


wherein  $R^3$  is as defined above.

3. A process for preparing a dermatologic preparation containing an amide derivative as prepared in claim 1 or 2 which comprises blending an acceptable base with the amide derivative.

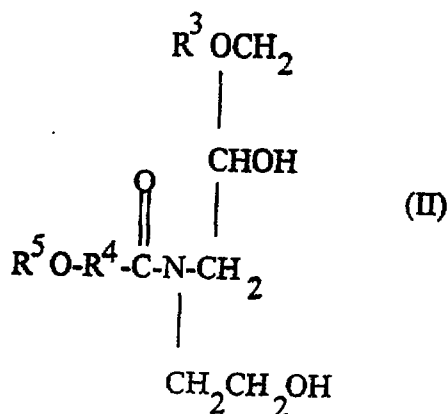
**Patentansprüche****Patentansprüche für folgende Vertragsstaaten : AT, CH, DE, FR, GB, LI, NL**

1. Amidderivat, dargestellt durch die folgende allgemeine Formel (I):



worin  $R^1$  und  $R^2$  jeweils eine geradkettige oder verzweigte, gesättigte oder ungesättigte Kohlenwasserstoffgruppe darstellen, mit der Maßgabe, daß eine von diesen 26 bis 39 Kohlenstoffatome aufweist, während die andere 9 bis 39 Kohlenstoffatome aufweist.

2. Amidderivat, dargestellt durch die folgende allgemeine Formel (II):



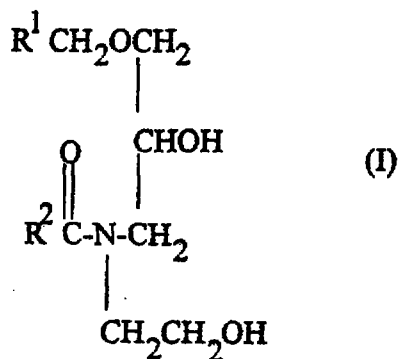
worin  $R^3$  eine geradkettige oder verzweigte, gesättigte oder ungesättigte Kohlenwasserstoffgruppe mit 10 bis 40 Kohlenstoffatomen darstellt;  $R^4$  eine geradkettige oder verzweigte Kohlenwasserstoffgruppe mit 3 bis 39 Kohlenstoffatomen darstellt; und  $R^5$  ein Wasserstoffatom, eine geradkettige oder verzweigte, gesättigte oder ungesättigte Kohlenwasserstoffgruppe mit 10 bis 40 Kohlenstoffatomen oder eine geradkettige oder verzweigte, gesättigte oder ungesättigte Acylgruppe mit 10 bis 40 Kohlenstoffatomen darstellt.

3. Dermatologisches Mittel, enthaltend ein Amidderivat nach Anspruch 1 oder 2.

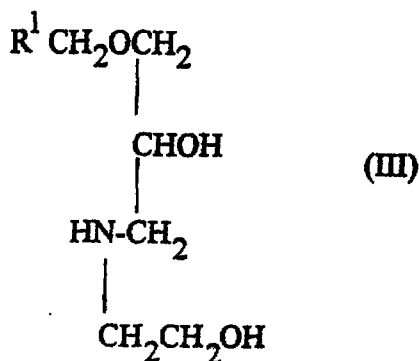


Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zum Herstellen eines Amidderivats, dargestellt durch die folgende allgemeine Formel (I):

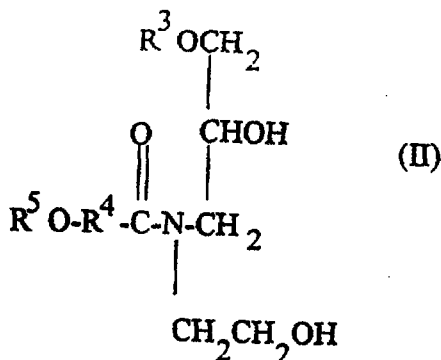


worin  $R^1$  und  $R^2$  jeweils eine geradkettige oder verzweigte, gesättigte oder ungesättigte Kohlenwasserstoffgruppe darstellen, mit der Maßgabe, daß eine von diesen 26 bis 39 Kohlenstoffatome aufweist, während die andere 9 bis 39 Kohlenstoffatome aufweist, welches das Reagierenlassen einer Verbindung der Formel (III)



worin  $R^1$  wie vorstehend definiert ist, mit einem Fettsäure-niederem Alkyl-Ester der Formel  $R^2 CO_2 R^6$ , worin  $R^2$  wie vorstehend definiert ist und  $R^6$  eine  $C_{1-5}$  Alkylgruppe ist, in Anwesenheit eines Basekatalysators umfaßt.

2. Verfahren zum Herstellen eines Amidderivats, dargestellt durch die folgende allgemeine Formel (II):

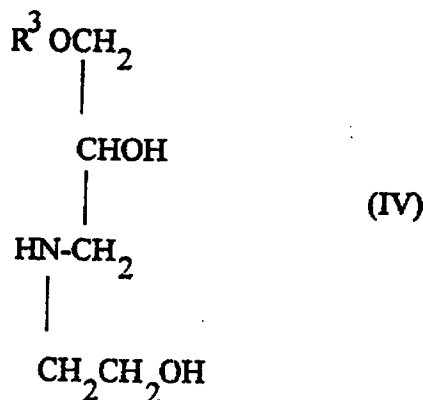


worin  $R^3$  eine geradkettige oder verzweigte, gesättigte oder ungesättigte Kohlenwasserstoffgruppe mit



10 bis 40 Kohlenstoffatomen darstellt;  $R^4$  eine geradkettige oder verzweigte Kohlenwasserstoffgruppe mit 3 bis 39 Kohlenstoffatomen darstellt; und  $R^5$  ein Wasserstoffatom, eine geradkettige oder verzweigte, gesättigte oder ungesättigte Kohlenwasserstoffgruppe mit 10 bis 40 Kohlenstoffatomen oder eine geradkettige oder verzweigte, gesättigte oder ungesättigte Acylgruppe mit 10 bis 40 Kohlenstoffatomen darstellt, welches

(a) das Reagierenlassen eines Aminderivats der Formel (IV)



worin  $R^3$  wie vorstehend definiert ist, mit einem Hydroxyfettsäure-niederem Alkyl-Ester der Formel (V-A) oder einem Hydroxyfettsäure-Lacton der Formel (VI)



worin  $R^3$  und  $R^4$  wie vorstehend definiert sind, und  $R^7$  eine  $C_{1-5}$ -Alkylgruppe ist, in Anwesenheit eines Basekatalysators; oder

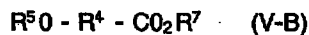
(b) das Reagierenlassen einer Hydroxyfettsäure der Formel (V) oder eines Hydroxyfettsäureesters der Formel (V-A)



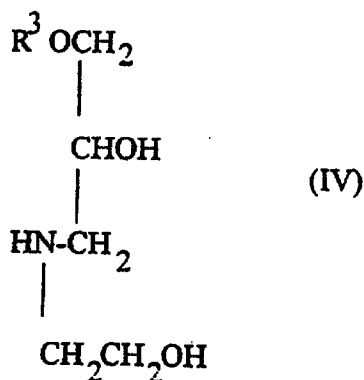
worin  $R^4$  wie vorstehend definiert ist und  $R^7$  eine  $C_{1-5}$ -Alkylgruppe ist, mit einem Alkylhalogenid der Formel (VII) oder einem Alkylsulfonat der Formel (VIII)



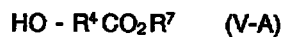
worin  $R^5$  eine geradkettige oder verzweigte, gesättigte oder ungesättigte  $C_{10-40}$ -Kohlenwasserstoffgruppe ist;  $R^8$  Methyl, Phenyl oder p-Tolyl ist; und X Cl, Br oder I ist; in Anwesenheit einer Base, um einen veretherten Fettsäureester der Formel (V-B)



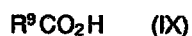
zu erhalten, worin  $R^4$ ,  $R^5$  und  $R^7$  wie vorstehend definiert sind; und weiterhin das Reagierenlassen mit einem Amidderivat der Formel (IV)



worin  $R^3$  wie vorstehend definiert ist, in Anwesenheit eines Basekatalysators, oder  
(c) das Kondensieren eines Hydroxyfettsäureesters der Formel (V-A)



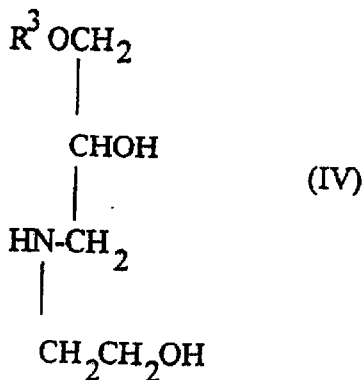
worin  $R^4$  und  $R^7$  wie vorstehend definiert sind,  
mit einer Fettsäure der Formel (IX)



worin  $R^9$  eine geradkettige oder verzweigte, gesättigte oder ungesättigte  $C_3$ - $_{39}$ -Kohlenwasserstoff-  
gruppe ist,  
in Anwesenheit eines Dehydratisierungsmittels, um einen acylierten Fettsäureester der Formel (V-C)



zu erhalten, worin  $R^4$ ,  $R^7$  und  $R^9$  wie vorstehend definiert sind,  
der dann in Anwesenheit eines Basekatalysators mit einem Amidderivat der Formel (IV)



reagiengelassen wird, worin  $R^3$  wie vorstehend definiert ist, umfaßt.

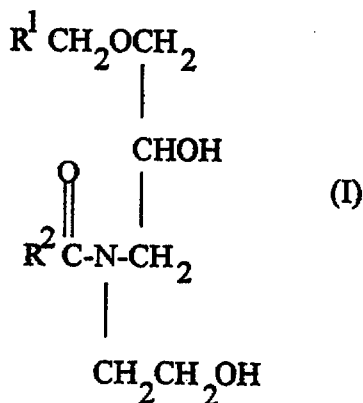
3. Verfahren zum Herstellen eines dermatologischen Mittels, enthaltend ein Amidderivat, hergestellt nach Anspruch 1 oder 2, welches das Mischen einer annehmbaren Base mit dem Amidderivat umfaßt.



# Revendications

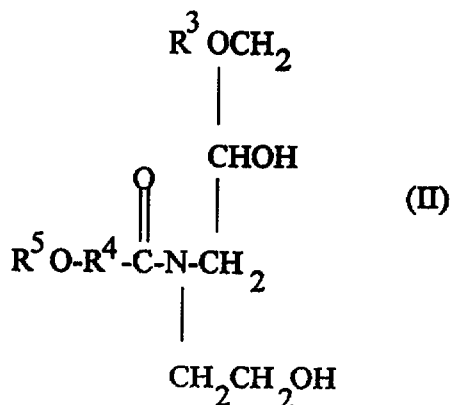
Revendications pour les Etats contractants suivants : AT, CH, DE, FR, GB, LI, NL

1. Dérivé d'amide représenté par la formule générale (I) suivante :



où  $R^1$  et  $R^2$  représentent chacun un groupe hydrocarboné saturé ou insaturé, à chaîne linéaire ou ramifiée, à condition que l'un d'eux porte 26 à 39 atomes de carbone tandis que l'autre porte 9 à 39 atomes de carbone.

2. Dérivé d'amide représenté par la formule générale (II) suivante :

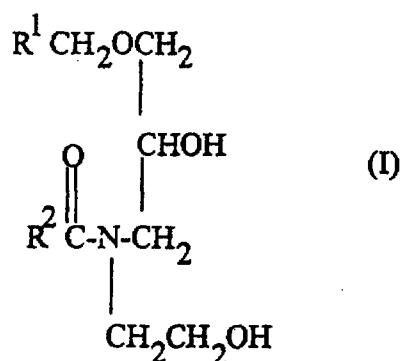


où  $R^3$  représente un groupe hydrocarboné saturé ou insaturé, à chaîne linéaire ou ramifiée, portant 10 à 40 atomes de carbone ;  $R^4$  représente un groupe hydrocarboné à chaîne linéaire ou ramifiée, portant 3 à 39 atomes de carbone ; et  $R^5$  représente un atome d'hydrogène, un groupe hydrocarboné saturé ou insaturé, à chaîne linéaire ou ramifiée, portant 10 à 40 atomes de carbone, ou un groupe acyle saturé ou insaturé, à chaîne linéaire ou ramifiée, portant 10 à 40 atomes de carbone.

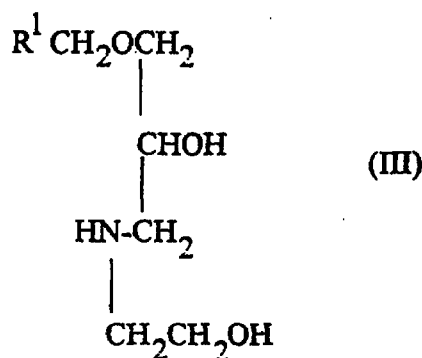
3. Préparation dermatologique contenant un dérivé d'amide selon la revendication 1 ou 2.


**Revendications pour l'Etat contractant suivant : ES**

1. Procédé de préparation d'un dérivé d'amide représenté par la formule générale (I) suivante :

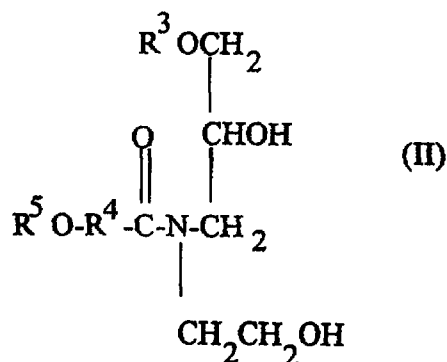


où  $R^1$  et  $R^2$  représentent chacun un groupe hydrocarboné saturé ou insaturé, à chaîne linéaire ou ramifiée, à condition que l'un d'eux porte 26 à 39 atomes de carbone tandis que l'autre porte 9 à 39 atomes de carbone, qui comprend la réaction d'un composé de formule (III)



où  $R^1$  est tel que défini ci-dessus, avec un ester alkylique inférieur d'acide gras de formule  $R^2 CO_2 R^6$ , où  $R^2$  est tel que défini ci-dessus et  $R^6$  est un groupe alkyle en  $C_1$  à  $C_5$ , en présence d'un catalyseur basique.

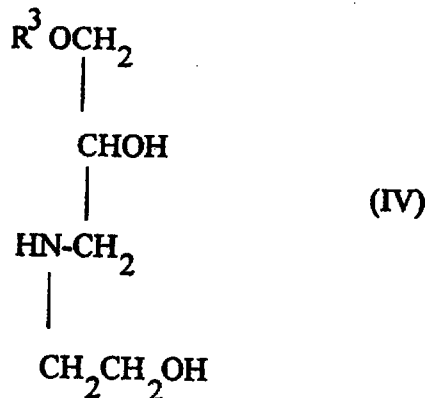
2. Procédé de préparation d'un dérivé d'amide représenté par la formule générale (II) suivante :



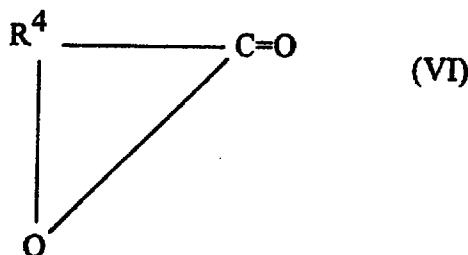
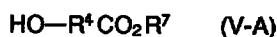
où  $R^3$  représente un groupe hydrocarboné saturé ou insaturé, à chaîne linéaire ou ramifiée, portant 10 à 40 atomes de carbone ;  $R^4$  représente un groupe hydrocarboné à chaîne linéaire ou ramifiée, portant



3 à 39 atomes de carbone ; et R<sup>5</sup> représente un atome d'hydrogène, un groupe hydrocarboné saturé ou insaturé, à chaîne linéaire ou ramifiée, portant 10 à 40 atomes de carbone, ou un groupe acyle saturé ou insaturé, à chaîne linéaire ou ramifiée, portant 10 à 40 atomes de carbone, qui comprend  
(a) la réaction d'un dérivé d'amine de formule (IV)

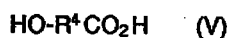


où R<sup>3</sup> est tel que défini ci-dessus, avec un ester alkylque inférieur d'hydroxy acide gras de formule (V-A) ou une hydroxy lactone d'acide gras de formule (VI)

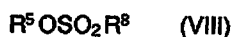


où R<sup>3</sup> et R<sup>4</sup> sont tels que définis ci-dessus et R<sup>7</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>5</sub>, en présence d'un catalyseur basique ; ou

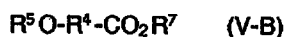
(b) la réaction d'un hydroxy acide gras de formule (V) ou d'un ester d'hydroxy acide gras de formule (V-A)



où R<sup>4</sup> est tel que défini ci-dessus et R<sup>7</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>5</sub>, avec un halogénure d'alkyle de formule (VII) ou un sulfonate d'alkyle de formule (VIII)



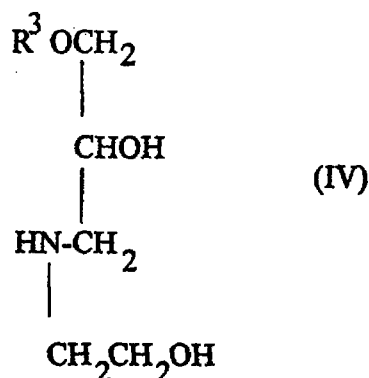
où R<sup>5</sup> est un groupe hydrocarboné en C<sub>10</sub> à C<sub>40</sub> saturé ou insaturé, à chaîne linéaire ou ramifiée ; R<sup>8</sup> est un groupe méthyle, phényle ou p-tolyle ; et X est Cl, Br ou I ; en présence d'une base, pour obtenir un ester d'acide gras étherifié de formule (V-B)



où R<sup>4</sup>, R<sup>5</sup> et R<sup>7</sup> sont tels que définis ci-dessus ; et ensuite la réaction avec un dérivé d'amide de



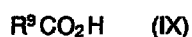
formule (IV)



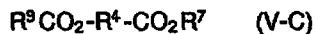
où  $R^3$  est tel que défini ci-dessus, en présence d'un catalyseur basique, ou  
(c) la condensation d'un ester d'hydroxy acide gras de formule (V-A)



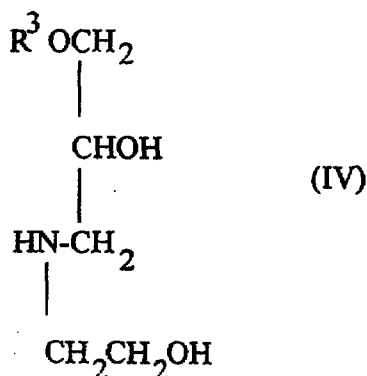
où  $R^4$  et  $R^7$  sont tels que définis ci-dessus,  
avec un acide gras de formule (IX)



où  $R^9$  est un groupe hydrocarboné en  $C_3$  à  $C_{39}$  saturé ou insaturé, à chaîne linéaire ou ramifiée,  
en présence d'un agent déshydratant pour donner un ester d'acide gras acylé de formule (V-C)



où  $R^4$ ,  $R^7$  et  $R^9$  sont tels que définis ci-dessus,  
qu'on fait ensuite réagir en présence d'un catalyseur basique avec un dérivé d'amide de formule  
(IV)



où  $R^3$  est tel que défini ci-dessus.

3. Procédé pour préparer une préparation dermatologique contenant un dérivé d'amide tel que préparé dans la revendication 1 ou 2, qui comprend le mélange d'une base acceptable avec le dérivé d'amide.