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THERAPEUTIC PREPARATIONS FOR TOPICAL APPLICATION TO THE SKIN

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20 Claims. (Cl. 167—87)

This invention pertains to therapeutic compositions and more particularly to compositions for the treatment of dermatological disorders of the scalp and other epithelial areas of the body.

The scalp condition commonly referred to as "dandruff" and medically known by the generic term pityriasis is of general occurrence and is found in several forms and many degrees of severity. Despite widespread interest in the nature and causes of dandruff extending over many years in the past, there is still no agreement among dermatologists as to the number or importance of the causative factors.

A prevalent theory is that this condition is the result of a normal physiological process, i.e., the flaking of the superficial areas of dead epithelial tissue. It is known that the cells over the entire epidermal surface of the human body continuously die and, in the process of replacement by the regeneration of new tissue, are sloughed off. Generally such dead tissue is removed, unnoticed by the individual, in the normal course of daily activities, as by bathing or the slight abrading action of the clothing. However, in the case of the scalp, loss of such dead tissue is prevented by mixture with the oily secretions of the skin and retention by the hair. According to this theory, observed differences in the quantity and appearance of dandruff in different individuals is due only to the differences in the normal physiological processes of those individuals.

Another common theory is that pityriasis or dandruff is caused by one or more microbiological organisms of a pathogenic or saprophytic nature. Despite the fact that an appreciable microbiological flora is associated with the normal human scalp, investigations have revealed that many abnormal scalp conditions, with or without visible scalp irritation or lesions, are accompanied by an increase in the numbers of one or more types of organisms as determined by standard microbiological culture techniques. Against this theory is the inability up to the present time to transfer from one individual to another, by known culture methods, the disorders loosely grouped under the term dandruff. Thus, although certain clinically identifiable scalp disorders are generally accompanied by the presence of greater or lesser numbers of a particular organism or group of organisms, the importance of this factor is not well known. Nevertheless, in part because of the lack of a better standard, many investigators have used the microbiological culture technique as a means of measuring the value of medicinal compositions for treatment of diseases of the scalp.

Among the more common scalp disorders, the following may be mentioned as being of frequent occurrence: pityriasis sicca, pityriasis oleosa, pityriasis steatoides, pityriasis capitis, and seborrheic dermatitis. Commonly present in association with one or more of the foregoing diseases are the following organisms: certain species of the genus Mucor, certain species of the genus Aspergillus, certain of the yeast-like fungi such as Monolia and

Torula, *Pityrosporum ovale, Bacillus substilis, Staphylococcus aureus* and *Staphylococcus albus.*

Despite the lack of understanding of the cause of dandruff and similar scalp conditions, there have been in the past many attempts at treatment. Among the active ingredients which have been or are currently being utilized in therapeutic compositions of the prior art are elemental sulphur in a variety of forms as well as chemically combined sulphur in the form of polythionic acids, polythionates and certain sulfanilamide derivatives. Selenium compounds, such as selenium sulfide, have also appeared in prior art compositions of this general nature.

These prior attempts to control dermatological disorders of the aforementioned and similar types have, in general, proven unsatisfactory in one or more respects. Thus, compositions containing free sulphur have a disagreeable odor whereas selenium compounds are highly toxic and consequently must be used with extreme caution, as by incorporation into a shampoo which is removed shortly after application. Many compounds of the sulfanilamide type result in a sensitizing action thereby limiting their usefulness as therapeutic agents. Further, the prior art therapeutic compositions for treatment of the scalp generally possess poor hair grooming qualities. Even where one or more of these disadvantages have been partially overcome by the prior art, it often has been found that the condition under treatment was not amenable to such therapy or that the therapeutic agents were ineffective to appreciably reduce the severity of the condition except by frequent and extended application.

Therefore, a primary object of the present invention is to provide, for the effective treatment of disorders of the scalp and other epithelial areas, a therapeutic composition which does not have the objectionable features of prior art compositions.

Another object is to provide a therapeutic composition which is useful to cleanse the hair and scalp.

Another object is to provide a therapeutic scalp cleanser which may be safely used without supervision by a physician and which is compatible with soaps, detergents, hair dyes, hair grooming agents, wave set preparations and the like.

A still further object of the invention is to provide a therapeutic salve or ointment for the treatment of seborrheic conditions of the skin.

Yet another object is to provide a method for successful treatment of dandruff and related skin diseases.

Other objects and advantages of this invention will become apparent from an inspection of the following detailed description.

It is known that certain compounds containing the thionate radical, $S_nO_6^=$ possess a bactericidal and fungicidal action and are useful in the treatment of skin diseases when applied topically. Thus, Neesby, in United States Reissue Patent No. 23,711, discloses polythionic acids and alkali metal salts thereof having the formulae $R_2S_nO_6$ wherein R is an alkali metal cation and n is an integer from 4 to 6. Such compounds, i.e., the tetra-, penta- and/or hexathionic acids or thionates exert a physiological sulphur action but do not possess the many disadvantages inherent in elemental sulphur. They are water soluble and, in the form of aqueous solutions, are useful in the topical treatment of skin diseases.

The polythionic acids and polythionates, such as described by Neesby, are, however, insoluble in compositions having high alcohol contents. It is known that many hair grooming agents contain, as an essential ingredient thereof, a large percentage of alcohol. The present invention contemplates such a hair grooming composition

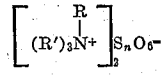
which is also effective as a therapeutic scalp composition in part by reason of the incorporation therein of an alcohol-soluble derivative of any one of a number of or a mixture of polythionic acids or polythionates.

The alkali metal salts of polythionic acids may be chemically combined with halogenated amines to yield alcohol-soluble amine salts. For example, the products of the reaction between alkali metal polythionates and halogenated primary, secondary and tertiary amines are contemplated. As products of such contemplated reactions, there may be mentioned tetradecylamine polythionates, the 2, 2′, diethyldihexylamine salt of polythionic acids and the dimethyloctadecylamine salt of polythionic acids. Illustrative of such compounds is the reaction product of the sodium salts of a mixture of polythionates such as described by Neesby and a quaternary ammonium halide. Thus

$$Na_2S_nO_6+2[(R)_4N^+]X^-\rightarrow[(R)_4N^+]_2S_nO_6=+2NaX \quad (I)$$

where n is an integer from 4 to 6, X represents a halogen, and R represents an alkyl group having from 1 to 24 and preferably from 12 to 18 carbon atoms, an aryl group, a hydroaryl (cycloaliphatic) group, an aralkyl group or an alkyl hydroaryl group wherein the alkyl moiety, in each instance, has from 1 to 3 carbon atoms, or any combinations thereof.

The products of such reactions can be written, in a more specific form, as



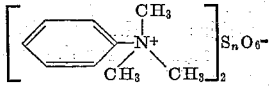
(II)

where R′ represents an alkyl group having from 1 to 10 carbon atoms, and R is the same as in the general formula in Equation I, except that the alkyl group contains preferably from 6 to 24 carbon atoms.

It should be noted that in any particular compound, it is not necessary that all groups denoted by R or R′ have the same structure. Any combination of the specified structures is suitable.

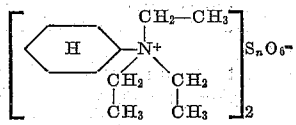
Illustrative of products which may result from reactions of this type are:

Phenyltrimethylammonium polythionate



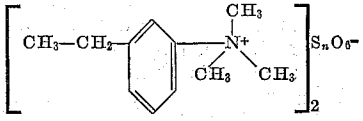
(III)

Triethylcyclohexylammonium polythionate



(IV)

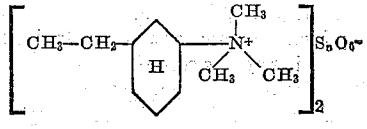
Phenylethyltrimethylammonium polythionate



(V)

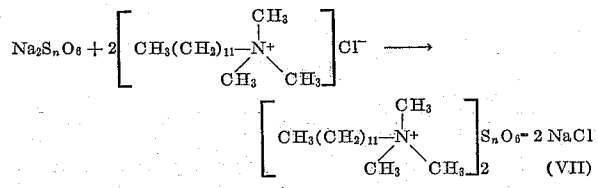
or

Ethylcyclohexyltrimethylammonium polythionate



(VI)

A preferred reaction is that between a mixture of sodium polythionates and dodecylthrimethylammonium chloride. Thus,

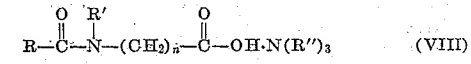


(VII)

The product of the above reaction, dodecyltrimethylammonium polythionate, is highly alcohol-soluble.

Quaternary ammonium polythionates, such as dodecyltrimethylammonium polythionates, utilizable for the purposes of the present invention are available commercially in the form of a viscous, syrupy mass having an acidic reaction and containing a maximum of about 10% by weight of water and about 32 to 35% by weight of total polythionate.

It has now been discovered that skin diseases such as those previously described, are surprisingly responsive to the above-described alcohol-soluble polythionate salts when topically applied in conjunction with an amine salt of certain acylated amino acids or alkyl N-substituted derivatives thereof. The amino acid derivatives contemplated by this invention may have compositions as indicated by one of the following formulae:



(VIII)

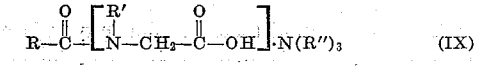
wherein:

R represents an alkyl group having from 6 to 24 and preferably from 12 to 18 carbon atoms;

R′ represents H or an alkyl group having from 1 to 5 carbon atoms;

R″ represents H, an alkyl group having from 1 to 24 and preferably from 12 to 18 carbon atoms, an aryl group, a hydroaryl, commonly known as cycloaliphatic, group, an aralkyl group, or an alkyl hydroaryl group wherein the alkyl portion, in each instance, has from 1 to 3 carbon atoms, or any combination thereof, and n is an integer 1 or 2;

or

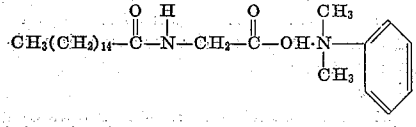


(IX)

wherein R, R′ and R″ represent the same respective groups as in Formula VIII above, and the portion of the formula within the brackets [] may be replaced by any other amino acid moiety.

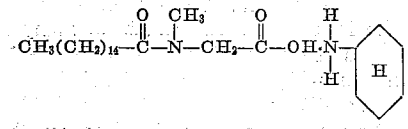
As examples of compounds having formulae according to VIII or IX, above, the following may be mentioned:

The dimethyl aniline salt of palmitoyl glycine,



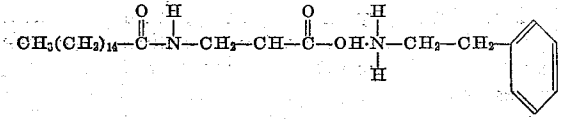
(X)

The cyclohexylamine salt of palmitoyl sarcosine,



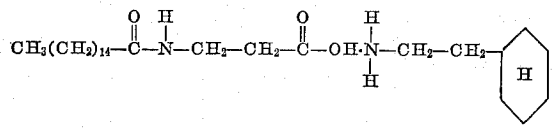
(XI)

The β-phenylethyl amine salt of palmitoyl β-alanine,



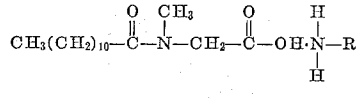
(XII)

The β-cyclohexylethylamine salt of palmitoyl β-alanine,



(XIII)

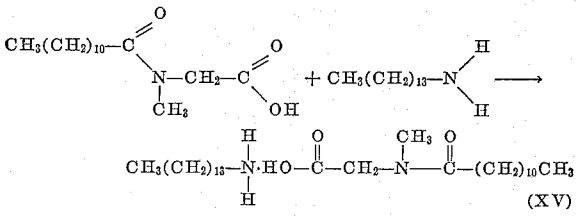
Illustrative of a preferred class of amino acid derivatives are aliphatic amine salts of N-lauroyl sarcosinate



(XIV)

where R is an alkyl group having from 6 to 24 carbon atoms and preferably from 12 to 18 carbon atoms.

An example of a preferred amino acid derivative is tetradecylammonium lauroyl sarcosinate which may be prepared by reacting N-lauroyl sarcosinate with tetradecylamine according to the following formula:



(XV)

Compounds such as the above are highly soluble in ethyl alcohol.

A preferred composition containing both of the above types of compounds as active or therapeutic ingredients may be illustrated by the following example.

EXAMPLE 1

Liquid formulation

Component:	Weight percent
Dodecyltrimethylammonium polythionate	3
Tetradecylammonium lauroyl sarcosinate	0.5
Ethyl alcohol (95%)	75
Water	21.5

Because of the insolubility of the therapeutic agents in water, it is necessary, in order to obtain their complete solution, to have a minimum alcohol content of about 65%. The solvent phase of the therapeutic composition may comprise as much as 100% of 95% alcohol.

The concentrations of the active ingredients, for example, dodecyltrimethylammonium polythionate and tetradecylammonium lauroyl sarcosinate as in Example 1, above, may be increased if desired to the limits of their respective solubilities which are known to be higher than those specified in Example 1.

There may be added to the above compositions varying amounts of water- and alcohol-soluble grooming agents such as a butyl ether of polypropylene glycol or vegetable oils such as castor oil. The total amount of such ingredients may comprise from 0 to about 20% of the total composition. An acceptable hair grooming product has been found to be one having the composition of Example 1 above except that the water content is decreased to 16.5% and 5% of "Ucon" (a butyl ether of polypropylene glycol is added). Preferably the pH of the composition is adjusted to approximate that of the scalp.

In the process of manufacture of the liquid therapeutic compositions of this invention, the two therapeutic components, together with a grooming material and a perfume (if included), are dissolved in the alcohol. The water (if included) is then added and the pH is adjusted by the addition of a suitable acid or base. Finally, the product is clarified by filtration.

The polythionate salts and the amino acid derivatives contemplated by this invention may also be utilized in

compositions wherein the solvent phase is comprised wholly or partially of solvents other than ethyl alcohol or ethyl alcohol-water mixtures. Such other solvents must also be non-toxic, non-sensitizing, non-irritant, compatible with soaps, detergents, etc., and are exemplified by isopropyl alcohol, certain glycols, such as dipropylene glycol, propylene glycol, polypropylene glycol "200," certain polyethylene glycol esters, such as polyethylene glycol "400" monolaurate or certain sorbitol derivatives of polyethylene glycol such as Atlas Powder Company product G–2004.

The therapeutic ingredients contemplated by the present invention may also be incorporated into a salve or ointment for topical application in the treatment of skin diseases. Such an ointment may comprise an emulsion having water as the principal component of the continuous phase and including, as the disperse phase, a suitable inert oil together with the therapeutic components. Suitable emulsifiers, preservatives, diluents, humectants, etc., may be added as desired. The following example is illustrative of a preferred ointment composition.

EXAMPLE 2

Ointment formulation

Component:	Parts by weight
Stearic acid	11.7
Petrolatum	14.3
Sorbitan stearate	4.7
A polyoxyethylene stearate (Atlas Powder Company G–2151)	4.7
Propylene glycol	4.7
Methyl p-hydroxy benzoate	0.11
Propyl p-hydroxy benzoate	0.01
Tetradecylammonium lauroyl sarcosinate	2.0
Dodecyltrimethylammonium polythionate	5.0
Water	52.78

In Example 2, stearic acid and petrolatum, together with the therapeutically active ingredients, i.e., tetradecylammonium lauroyl sarcosinate and dodecyltrimethylammonium polythionate, constitute the disperse phase of the emulsion and water as the principal component of the continuous phase. Propylene glycol serves as an humectant and the benzoates are preservatives.

In compounding a formulation as in Example 2, the water, propylene glycol and methyl p-hydroxy benzoate are mixed and heated to about 75° C. The remaining ingredients are mixed in another batch and heated to the same temperature whereby the solid or semi-solid components are melted and the therapeutic agents, being oil-soluble to an extent, are dissolved or suspended therein. The separate batches are then mixed, with agitation, and allowed to cool.

Ointment formulations of the general character of Example 2 may contain up to a total of about 30% of the therapeutic ingredients. Various substitutions and additions may be made in the case of the non-therapeutic components.

Both the polythionate derivatives and the amino acid derivatives contemplated by the present invention possess, to a slight extent, bactericidal and fungicidal properties. However, cultures of microbiological organisms obtained from scalps exhibiting clinical symptoms of the abnormal conditions under consideration herein have shown that the use of the compositions of this invention, wherein the polythionate derivatives and the amino acid derivatives are combined, result in a marked decrease of the numbers of one or more types of organisms associated with these abnormal conditions.

Likewise, neither the use of either component alone nor the non-concurrent use of both components on the same individual results in marked or unexpected effectiveness with respect to dandruff. However, when these two therapeutic agents are applied in conjunction with

one another the result is truly remarkable. Thus, laboratory studies carried out in the course of the present investigation, have shown that the amino acid derivative, when topically applied in an alcohol-containing solvent, has very little effect on scalp dandruff; similar use of the polythionate derivative alone does reduce dandruff, though not to nearly so great an extent as does the use of the combination of these two ingredients in the compositions of the present invention.

Clinical tests have been carried out on human subjects exhibiting all degrees of severity of dandruff and similar disorders. Such tests have utilized the polythionate component alone, the amino acid derivative alone, and the combination of the two, in each case the active ingredient or ingredients being dissolved in a solvent comprising either alcohol alone or alcohol plus water. Each individual was treated (non-concurrently) with each of these three compositions. The results were quite striking. Thus, by way of illustration, in cases of severe pityriasis of the scalp which had proven non-responsive to any other therapeutic agent, the separate use of the polythionate solution and the amine solution resulted in from two to four days' relief from scaling. On the other hand, application of the combined polythionate-amino acid derivative solution resulted in a three weeks' remission of all dandruff. This procedure has been tried on different subjects, always with similar results. Diagnoses of skin conditions of these subjects varied from pityriasis sicca and oleosa to seborrheic dermatitis associated with pityriasis. These results show that there is present a pronounced synergism when the two therapeutic agents are combined.

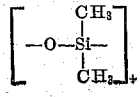
Additional tests of the combination product have conclusively shown its effectiveness in the rapid and prolonged control of dandruff and related disorders as well as its very appreciable superiority over any other known therapeutic composition used for the same purpose.

The compositions contemplated by the present invention are extremely safe in use. No sensitization or irritation of normal or abraded skin was observable during the course of safety tests of these compositions. This is a decided advantage over many prior art compositions.

Furthermore, the therapeutic compositions of the present invention exhibit no deleterious effect on the hair. There is no embrittlement, undue softening or discoloration such as results from the use of many of the compositions of the prior art. The compositions of the present invention are compatible with commercially available soaps, detergents, shampoos, hair dyes, hair grooming agents, wave set preparations and the like. They do not exhibit the objectionable odors so commonly associated with many prior art preparations.

The liquid preparations of the present invention may be applied to the hair and scalp without unduly interfering with the normal activity of the individual. Thus, the therapeutic scalp preparation contemplated by the present invention may be applied before washing the hair or it may be applied at any time and allowed to remain on the hair for prolonged periods. The latter procedure is particularly desirable when a separate grooming agent has been added.

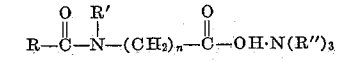
The mild detergent action of the amino acid derivatives contemplated by this invention lends to these therapeutic compositions the properties of self-shampoos, although the foaming action is not markedly pronounced. Formulations may be made for use as shampoos wherein ordinary types of soaps or detergents are added to produce more thorough dirt- and oil-removing action. If the slight foaming action of my compositions is undesirable, this action may be modified by the addition of a silicone foam inhibitor of a type having the general formula



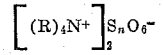
It is to be understood that the specific illustrations and examples described herein are not to be construed as limitations upon the present invention and that modifications or additions may be made by those skilled in the art without departing from the spirit and scope of the invention as defined in the appended claims.

What is claimed is:

1. A synergistic therapeutic composition for the treatment of skin diseases comprising a compound having the formula



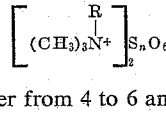
where n represents an integer 1 to 2, R is selected from the group consisting of alkyl radicals having from 6 to 24 carbon atoms, R′ is selected from the group consisting of H and an alkyl radical having from 1 to 5 carbon atoms and R″ is selected from the group consisting of H, an alkyl radical having from 1 to 24 carbon atoms, an aryl radical, a hydroaryl radical, an aralkyl radical, an alkyl hydroaryl radical and combinations thereof, wherein the alkyl moiety in said aralkyl radical and said alkyl hydroaryl radical contains from 1 to 3 carbon atoms, and a compound having the formula



where n represents an integer from 4 to 6, and R is an alkyl radical having from 1 to 24 carbon atoms.

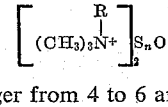
2. A therapeutic composition for the treatment of diseases of the skin comprising an amine salt of an acylated amino acid selected from the group consisting of glycine, alanine, beta-alanine and sarcosine wherein the acyl portion of the molecule contains an aliphatic group having from 6 to 24 carbon atoms, a mixture of alkyl amine salts of polythionic acids having the formula $H_2S_nO_6$ where n is an integer from 4 to 6, and a solvent for all of said salts.

3. A therapeutic composition for the treatment of skin diseases comprising an aliphatic amine salt of an acylated derivative of sarcosine wherein the acyl portion of said salt contains an aliphatic group having from 6 to 24 carbon atoms and each substituent of the aliphatic amine portion of the molecule contains from 1 to 24 carbon atoms, quaternary ammonium polythionates having the formula



where n is an integer from 4 to 6 and R is an alkyl group having from 6 to 24 carbon atoms, and a solvent for said salt and said polythionates.

4. A therapeutic composition for the treatment of diseases of the skin comprising an aliphatic amine salt of N-lauroyl sarcosinate, quaternnary ammonium polythionates having the formula



where n is an integer from 4 to 6 and R is an alkyl group having from 6 to 24 carbon atoms, and a solvent for said salt and said polythionates.

5. A synergistic composition for the therapeutic treatment of skin diseases comprising tetradecylamine lauroyl sarcosinate and dodecyltrimethylammonium polythionates.

6. A therapeutic composition for the treatment of skin diseases comprising tetradecylamine lauroyl sarcosinate, dodecyltrimethylammonium polythionates, and a solvent.

7. A therapeutic composition for the treatment of skin diseases comprising tetradecylamine lauroyl sarcosinate, dodecyltrimethylammonium polythionates, and an alcohol-containing solvent.

8. A therapeutic ointment for the treatment of skin diseases comprising tetradecylammonium lauroyl sarcosinate, dodecyltrimethylammonium polythionates, and an inert vehicle for said sarcosinate and said polythionates.

9. A therapeutic ointment for the treatment of skin diseases comprising an aliphatic amine salt of an amino acid amide, aliphatic amine salts of a mixture of tetra-, penta-, and hexathionic acids, and a suitable vehicle therefor.

10. An emulsion having therapeutic properties and comprising a continuous phase consisting substantially of water, and a disperse phase including an inert oil, an amine salt of an amino acid amide and an amine salt of a polythionic acid.

11. A therapeutic emulsion comprising a continuous phase consisting substantially of water, and a disperse phase including petrolatum, tetradecylammonium lauroyl sarcosinate and dodecyltrimethylammonium polythionate.

12. A combined therapeutic and hair grooming composition comprising a solute including tetradecylamine lauroyl sarcosinate, dodecyltrimethylammonium polythionates, a butyl ether of polypropylene glycol, and a solvent for said solute.

13. A therapeutic composition for the treatment of skin diseases comprising an amine salt of a compound selected from the group consisting of acylated amino acids and alkyl N-substituted derivatives thereof wherein the acyl portion of said compound contains an aliphatic group having from 6 to 24 carbon atoms, said amino acid is selected from the group consisting of glycine, alanine, beta-alanine and sarcosine and the alkyl substituent of said amino acid derivative contains from 1 to 5 carbon atoms, a quaternary ammonium polythionate having the formula

$$\left[(R)_4N^+\right]_2 S_nO_6^=$$

where n represents an integer from 4 to 6, R is an alkyl radical having from 1 to 24 carbon atoms, and a solvent for said salt and said polythionate.

14. A therapeutic composition for the treatment of skin diseases comprising an amine salt of a compound selected from the group consisting of acylated amino acids and alkyl N-substituted derivatives thereof wherein the acyl portion of said compound contains an aliphatic group having from 6 to 24 carbon atoms, said amino acid is selected from the group consisting of glycine, alanine, beta-alanine and sarcosine and the alkyl substituent of said amino acid derivative contains from 1 to 5 carbon atoms, a quaternary ammonium polythionate having the formula

$$\left[\begin{array}{c} R \\ | \\ (R')_3N^+ \end{array}\right]_2 S_nO_6^=$$

where n represents an integer from 4 to 6, R is an alkyl radical having from 6 to 24 carbon atoms and R' is an alkyl radical having from 1 to 10 carbon atoms, and a solvent for said salt and said polythionate.

15. The composition of claim 14 wherein R' represents the methyl group, CH_3.

16. The composition of claim 15 wherein R is an alkyl group having from 12 to 18 carbon atoms.

17. A therapeutic composition for the treatment of skin diseases comprising an aliphatic amine salt of a compounds selected from the group consisting of an acylated amino acid and alkyl N-substituted derivatives thereof wherein the acyl portion of said compound contains an aliphatic group having from 6 to 24 carbon atoms, said amino acid is selected from the group consisting of glycine, alanine, beta-alanine and sarcosine and the alkyl substituent of said amino acid derivative contains from 1 to 5 carbon atoms, dodecyltrimethyl ammonium polythionates, and a solvent for said salt and said polythionates.

18. A therapeutic composition for the treatment of skin diseases comprising an amine salt of an acylated derivative of sarcosine wherein the acyl portion of said derivative contains an aliphatic group having from 6 to 24 carbon atoms, a quaternary ammonium polythionate, and a solvent for said salt and said polythionate.

19. A therapeutic composition for the treatment of skin diseases comprising an aliphatic amine salt of an acylated derivative of sarcosine wherein the acyl portion of said derivative contains an aliphatic group having from 6 to 24 carbon atoms, dodecyltrimethyl ammonium polythionates, and an alcoholic solvent for said salt and said polythionates.

20. A therapeutic composition for the treatment of skin diseases comprising an amine salt of a compound selected from the group consisting of an acylated amino acid and alkyl N-substituted derivatives thereof wherein the acyl portion of said compound contains an aliphatic group having from 6 to 24 carbon atoms, said amino acid is selected from the group consisting of glycine, alanine, beta-alanine and sarcosine and the alkyl substituent of said amino acid derivative contains from 1 to 5 carbon atoms, an alkyl amine salt of a polythionic acid wherein each alkyl substituent of said polythionic acid salt contains from 1 to 24 carbon atoms, and a solvent for said salts.

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