United States Patent [19]

van Ham

[11] **3,907,580**

[45] **Sept. 23, 1975**

[54] **NAIL VARNISHES**

[75] Inventor: **Goswin Clemens van Ham,** Wiesbaden-Bierstadt, Germany

[73] Assignee: **Margaret Astor AG,** Mainz, Germany

[22] Filed: **Mar. 14, 1973**

[21] Appl. No.: **341,040**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 305,850, Nov. 12, 1972, abandoned.

[52] **U.S. Cl.** **106/158;** 106/183; 106/195; 424/61; 424/359

[51] **Int. Cl.**.... **A61k 7/04;** C08b 21/12; C08b 21/14

[58] **Field of Search** 106/158, 195; 424/359, 424/61

[56] **References Cited**

UNITED STATES PATENTS

3,342,686	9/1967	Jewel	106/195

OTHER PUBLICATIONS

Chem. Abst., Vol. 75: 15,4,991j, 1971.

Schimmel Briefs, No. 358, Jan. 1965

Primary Examiner—Theodore Morris
Attorney, Agent, or Firm—Price, Heneveld, Huizenga & Cooper

[57] **ABSTRACT**

A nitrocellulose nail varnish containing at least one scleroprotein derivative selected from the group consisting of certain collagen hydrolysates, polypeptide esters, protein fatty acid condensates, and mixtures thereof. The novel nail varnish has a favorable effect on the properties of human nails and reduces and eliminates nail damage, even in the case of individuals with sensitive or easily damaged nails.

21 Claims, No Drawings

NAIL VARNISHES

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of my copending application, Ser. No. 305,850, filed Nov. 12, 1972, for NAIL VARNISHES, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to nitrocellulose nail varnishes with conventional additives such as plasticizers, dyes, pigments, and the like.

The use of nail varnishes for beautifying human nails on the hands and feet has long been a conventional cosmetic practice. The human nail comprises structural protein or scleroprotein which is hard and insoluble and is made up of keratine. The material is dead-like human hair. In contrast, the nail bed, lying directly under the nail, is the living matrix of the nail and is rich in blood capillaries (see S. Jellinek, Kosmetologie, Huthig Verlag Heidelberg, 1967).

With the help of nail varnishes, a generally colored shining film, impervious to water and air is applied to which particular effects can be given by certain additives such as iridescent materials or pigments. Generally, the use of nail varnish does not have any favorable or unfavorable physiological effects on the nail. However, in the case of a considerable number of consumers, there are certain obstacles to the constant use of nail varnishes. On the one hand, the nails can be harmed by the constant penetration of these varnishes, leading to brittleness and the tendency to split; while on the other hand, there are persons whose nails have these properties at the outset so that the use of nail varnish is not even possible. On working in and with alkaline solutions, wetting agents and detergents, the damage is emphasized.

Various experiments have been carried out for a number of years in various different directions to reduce the above defects. The addition of hard resins to the nail varnish only leads to a hardening of the varnish film and is only possible within certain limits because the film otherwise becomes brittle.

Formaldehyde makes possible a hardening of the nail keratine but is irritating and in certain cases may give rise to allergy. The use of fats and oils, lanoline and other materials, and also moistening substances in the form of nail oil or nail emulsion, has also been previously proposed. The use of a suspension of microscopic fibres for coating the nail with a protective layer has also been proposed. None of these preparations can, however, be incorporated in nail varnishes since they substantially impair the film properties of the varnishes. They are therefore used as preparations to be separately applied and are therefore expensive and complicated for the consumer.

In recent times, experiments have also been carried out with the purpose of bringing about an influence on the nail properties with the help of aqueous cosmetic preparations or those containing water/alcohol mixtures and containing amino acids and peptides as active substances. These preparations are, however, to be used in addition to the nail varnish and do not make up a component of the varnish itself. The results appear to be favorable, but again, the defect of having to apply the preparation separately is present, and the simultaneous application of the nail varnish and these aqueous preparations yields adverse effects.

SUMMARY OF THE INVENTION

The present invention provides a nail varnish which has a favorable effect on the properties of the nails, reduces the above-mentioned defects and makes possible the general use of nail varnishes for extended periods of time, even in the case of persons whose nails are inclined to break and split in many cases. The invention provides a nail varnish which protects the nail treated with it from damage by the varnish film, makes nails which have already been damaged insensitive to nail varnish and has a favorable influence on the nail growth tissue or nail bed.

The nail varnish of the present invention comprises a nitrocellulose nail varnish containing at least one scleroprotein derivative selected from the group consisting of:

a. a collagen hydrolysate of animal origin with a pH in the range of about from 3 to 7.5;

b. an ester produced by alcoholic esterification of polypeptides which have a salt content of from 0 to about 3 per cent and which are produced by acidic hydrolysis of scleroprotein, said esters having the general formula:

$$H_2N—CHR—CO$$
$$[HN—CHR—CO]_n—NH—CHR—COOALc$$

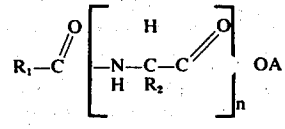
wherein:

R is an amino acid side chain

n is an integer between 3 and 300

Alc is an aliphatic group having 1 to 8 carbons atoms

c. a protein fatty acid condensate of the general formula:



wherein:

R_1 is a saturated or unsaturated hydrocarbon having from 8 to 17 carbon atoms and from 17 to 37 hydrogen atoms

R_2 is an amino acid side chain

n is an integer between 3 and 300

A is hydrogen, alkali metal, amine, or monovalent or polyvalent cation; and

d. mixtures thereof.

Preferably, the amount of hydrolysate is from about 0.05 to 6 per cent by weight of the nail varnish, the amount of ester is from about 0.05 to 6 per cent by weight of the nail varnish, and the amount of condensate is from about 0.05 to 4 per cent by weight of the nail varnish.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

According to the present invention, keratine substances and protein hydrolysates are directly worked in the nail varnish and, therefore, constantly supplied to the nail. Therefore, the unfavorable application of a separate nail-treating preparation is dispensed with and there is no impairment of the varnish film or the colors as produced by previously conventional nail hardeners such as formaldehyde or water- or oil-containing preparations.

In studying the scleroprotein derivatives such as proteins, keratines, scleroproteins and their reaction and decomposition products as used for cosmetic purposes and available in the trade, it was found that these substances were only suitable for use in aqueous or aqueous-alcoholic solutions. Thus, Messrs. Chem. Laborat. Dr. Richter, Berlin, sells "Collagen CLR" as a liquid concentrate for incorporation in the aqueous phase of cosmetic preparations for improving the elasticity of the human skin. Messrs. Croda Nippon Lts. represented by Croda G.m.b.H., Kaldenkirchen, Rheinland, sell protein hydrolysates under the name "Promois," which are used in shampoos, hair tonics, and other liquid hair-treating preparations.

Messrs. Chemische Fabrik Grunau of Illertissen produce protein fatty acid condensates under the name "Lamepon", which are provided for use in hydrophilic cosmetic cleaning preparations.

The fact that these protein compounds have only to date been used in conjunction with water for cosmetic application can be seen from the methods of production, for example acid hydrolysis in aqueous solution, and the strongly polar hydrophilic properties of the amino acid chains. It is known that protein compounds are precipitated by organic solvents or cannot be mixed with them.

My own tests with two typical nail varnish solvents such as toluol or ethylacetate showed that in the case of concentrations of 0.5 to 2 per cent there was in every case separation, denaturation, and precipitation of the amino compounds. It is therefore not surprising that all cosmetic successes described of a protein action on the skin or hair were in aqueous preparations such as hair tonic, shampoo, moistening emulsion or the like (see G. Schuster, H. Modde, E. Scheld in "Seifen, Öle, Fette, Wachse", reprint from issue No. 14 of 7th July, 1965; J. Cotte, B. Builott, H. Gattefosse, in "American perfumer & cosm.", 82, 47 (1967)).

It was discovered in numerous experimental series that the protein compounds proposed by the present invention can surprisingly be incorporated into nail varnishes containing nitrocellulose.

Thus, the nail varnish of the present invention comprises a nitrocellulose nail varnish containing at least one scleroprotein derivative selected from the group consisting of:

a. collagen hydrolysates of animal origin with a pH in the range of about from 3 to 7.5;

b. esters produced by alcoholic esterification of polypeptides which have a salt content of from 0 to about 3 per cent and which are produced by acidic hydrolysis of scleroprotein, said esters having the general formula:

$$H_2N—CHR—CO$$
$$[HN—CHR—CO]_n—NH—CHR—COOALc$$

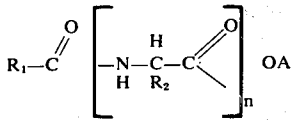
wherein:

R is an amino acid side chain

n is an integer between 3 and 300

Alc is an aliphatic group having 1 to 8 carbon atoms

c. protein fatty acid condensates of the general formula:



wherein:

R_1 is a saturated or unsaturated hydrocarbon having from 8 to 17 carbon atoms and from 17 to 37 hydrogen atoms

R_2 is an amino acid side chain

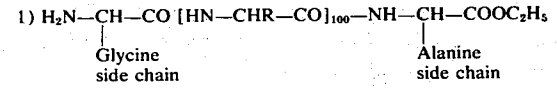
n is an integer between 3 and 300

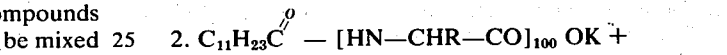
A is hydrogen, alkali metal, amine, or monovalent or polyvalent cation; and

d. mixtures thereof.

Preferably, the amount of hydrolysate is from about 0.05 to 6 per cent by weight of the nail varnish, the amount of ester is from about 0.05 to 6 per cent by weight of the nail varnish, and the amount of condensate is from about 0.05 to 4 per cent by weight of the nail varnish.

A preferred 1) ester and 2) condensate, respectively, are:





wherein:

R is a protein hydrolysate with the following contents of amino acids (average per cent by weight of protein): Lysine 5; Histidine 1; Arginine 7; Aspartic acid 5; Threonine 2; Serine 3; Glutamic acid 11; Proline 10; Glycine 17; Alanine 8; Valine 2; Methionine 2; Isoleucine 3; Leucine 3; Thyrosine 2; Phenylalanine 2; Hydroxylysine 2; Hydroxyproline 15.

Further representative examples of preferred scleroprotein derivatives which can be used in accordance with the invention are the substances sold under the trade names "Collagen CLR", "Promois A", "Lamepon S", "Lamepon ST-R" and "Lamepon 460". Collagen CLR is a liquid, aqueous solution of soluble embryonic calfskin protein, containing 300 gamma hydroxyproline per ml solution and with a pH value of 3.8. Promois A is the ethyl ester of a hydrolyzed collagen-derived polypeptide, supplied as a 25 per cent by weight solution in ethyl alcohol with a pH of 5.5 to 6.5, containing up to 0.3 per cent by weight of ammonium chloride. Lamepon S is the liquid condensation product of protein hydrolysate with plant fatty acids and neutralized with potassium hydroxide, supplied in aqueous 30 per cent by weight solution. Lamepon STR is similar to Lamepon S, except that neutralization is made with triethanolamine. Lamepon 460 is a mixture of Lamepon STR with fatty acid alkylolamides with 30 per cent of Lamepone STR and a pH value in aqueous solution of 6.5–6.9. The compositions of the Lamepon, Lamepon STR, and Lamepon 460, are described in the above referenced publication, G. Schuster et al., 7 July 1965 reprint and in Schimmel Brief No. 358 January 1965. The acyl chlorides used in the preparation of the Lamepon type of detergents are those of oleic acid or coconut fatty acids. In the presence of alkali fatty acid chloride reacts with free amine groups in the hydrolyzed protein forming fatty acid amide derivatives. The fatty acid alkanolamide used in Lamepon STR is lauric diethanolamide.

The above scleroprotein derivatives are dissolved in clear colorless nitrocellulose nail varnishes, with the

following concentrations by weight being especially preferred:

Collagen CLR	0.05 to 1.8	%
Promois A	0.05 to 5	%
Lamepon S	0.05 to 4	%
Lamepon 460	0.05 to 0.9	%
Lamepon ST-R	0.05 to 0.6	% clear
	0.8 to 2	% turbid
	2.5 to 4	% clear

("Clear" and "turbid" means that the nail varnish remains clear or becomes turbid after the addition.)

A representative example of a nitrocellulose nail varnish into which the scleroprotein derivatives can be incorporated according to the present invention by rapid stirring, in the concentrations given, has the following composition (hereinafter referred to as Varnish B);

Nitrocellulose E 510 with 18% by weight Dibutyl phthalate	16.50% by weight
Nitrocellulose E 730 with 18% by weight Dibutyl phthalate	1.00% by weight
Dibutyl phthalate	2.90% by weight
Santolite MHP resin (aryl sulfonamide-formaldehyde resin)	12.60% by weight
Camphor	3.40% by weight
Ethyl acetate	26.60% by weight
Butyl acetate	23.00% by weight
Toluol	14.00% by weight

Although dyes, whitening and brightening pigments, resins, plasticizers, solvents or other conventional nail varnish components can be added, they are not completely without influence on the solubility of the scleroprotein derivatives. For example, in the case of opaque nail varnishes containing coloring pigment and iridescent pigment, excessive concentrations of protein compounds can lead to loosening, decomposition and also changes in the color and viscosity of the varnishes. The following are examples of a typical iridescent nitrocellulose nail varnish (hereinafter referred to as Varnish D) and a typical colored nitrocellulose nail varnish:

	Iridescent Varnish (% by weight)	Colored Varnish (% by weight)
Clear varnish in accordance with Example 1	77.0	80.0
Pink dye solution of chips conc.	3.0	—
Corall dye solution of chips dil.	—	17.0
Nail varnish iridescent shining pigment Mearl Corpor., U.S.A.	16.5	—
Ethyl acetate	3.5	3.0
	100.0	100.0

In the above iridescent and colored varnishes, the following upper limits of the identified scleroprotein derivatives have been found to be especially preferred:

Scleroprotein Derivative	Iridescent Varnish (% by weight)	Colored Varnish (% by weight)
Collagen CLR	about 0.7	about 1
Promois A	about 1.5	about 3
Lamepon S	about 0.8	about 1.2
Lamepon 460	about 0.8	about 1
Lamepon STR	about 0.5	about 1

Nail varnishes containing nitrocellulose with additions of scleroprotein derivatives below the preferred concentration limits are stable and superior to protein-free nitrocellulose nail varnishes as has been shown in long-period storage tests. Tests on the nail varnishes produced in accordance with the invention showed that there was no change in the properties, color or clearness within 9 months at 20° C. in light or in the dark, within 2 months at 40°C., or at refrigerator temperatures. Further, a separation or precipitation of the protein compounds could not be observed.

The application of the nail varnishes produced in accordance with the present invention was tried out with various groups of test persons as set forth in the following examples:

EXAMPLE 1

To five 99 g samples of clear Varnish B, as identified above, were added with rapid stirring 0.9 g of Collagen CLR, Promois A, Lamepon S, Lamepon 460, and Lamepon ST-R, respectively. After the rise of the air bubbles to the surface, the material was placed in nail varnish bottles. Two groups of test persons were given bottles of each of the five keratine-containing nail varnishes, hereinafter referred to as Varnishes A, and a bottle of the keratine-free nail varnish, Varnish B.

The first test group, test group 1, consisted of test persons who use nail varnish continuously without any complaints. During the test, the Varnishes A and B were used simultaneously, with the Varnishes A being applied to the first, third, fifth, seventh, and ninth fingers, respectively, and Varnish B being applied to the second, fourth, sixth, eighth, and tenth fingers. Evaluation showed that there were better results with all of Varnishes A with respect to hardness and resistance to scratching. Further, in the case of dish washing, there was a more ready detachment and liability to become matt in the case of Varnish B. After leaving the varnishes on the fingers for 2 days and using the hands normally, the test persons found that there were more scratches and parts rubbed off with nails varnished with Varnish B, such damage being produced, for example, by moving the nails over the top of a table or knocking against the edges.

The second test group, test group 2, consisted of test persons who previously had to interrupt the use of nail varnish because after a certain time their nails would become damaged. The varnishes and manner of application were the same as used with test group 1. The evaluation of a test lasting 4 weeks showed that an interruption of the use of Varnishes A was not necessary since the nails did not become brittle or cracked. In one case, a breaking of the nails was still observed, but this only occurred after a long period of time. In the case of the use of Varnish B, the usual damage occurred in the period as previously experienced.

EXAMPLE 2

To five 99.4 g samples of the iridescent Varnish D, as identified above, were added 0.6 g of the five keratine substances used in Example 1, respectively, with strong stirring. After the air bubbles had escaped, the material was placed in nail varnish bottles (hereinafter referred to as Varnishes C) and, together with a bottle of Varnish D, given to the test persons in a third test group for testing in accordance with the scheme employed in Example 1.

This third test group, test group 3, consisted of two test persons who normally could not use any nail varnish because of the brittleness of their nails. Under the influence of all of the Varnishes C, a continuous improvement in the hardness properties of their nail growth was found. This was shown by the fact that the nails broke off less often, the length of the nails above the end of the finger before breaking increased, and after approximately 6 to 8 weeks, the nails became much more even than previously was the case. The Varnish D, free of keratine, was not tolerated by either test person.

The above tests showed that the use of scleroprotein derivatives in nitrocellulose nail varnishes in accordance with the present invention hardens the nails and makes them resistant (test group 1), prevents nail damage, and hardens the nail itself (test group 2) and improves inferior nail growth (test group 3).

While preferred embodiments of the present invention have been described, it will be obvious to those skilled in the art that various modifications can be made without departing from the spirit of the invention. Accordingly, the scope of the present invention is deemed to be limited only by the appended claims.

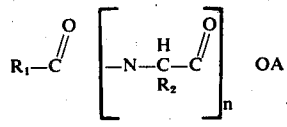
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. In a liquid nitrocellulose nail varnish containing organic solvents selected from the group consisting of ethyl acetate, butyl acetate toluol and mixtures thereof for the varnish, the improvement which comprises at least one scleroprotein derivative insoluble in varnish organic solvents alone and soluble in aqueous or aqueous-alcoholic solutions and in said nitrocellulose varnish and selected from the group consisting of:

a. between about 0.05 to 6 percent of a collagen hydrolysate of animal origin with a pH in the range of about from 3 to 7.5;

b. between about 0.05 and 6 percent of an ester produced by alcoholic esterification of polypeptides which have a salt content of from 0 to about 3 percent and which are produced by acidic hydrolysis of scleroprotein, said esters having the general formula: $H_2N—CHR—CO\ (HN—CHR—CO)_n—NH—CHR—COOALc$ wherein:
R is an amino acid side chain
n is an integer between 3 and 300
Alc is an aliphatic group having 1 to 8 carbon atoms;

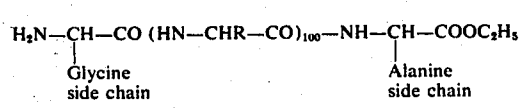
c. between about 0.05 and 4 percent of a protein fatty acid condensate of a general formula



wherein:
R_1 is a saturated or unsaturated hydrocarbon having from 8 to 17 carbon atoms and from 17 to 37 hydrogen atoms
R_2 is an amino acid side chain
n is an integer between 3 and 300
A is hydrogen, alkali metal, amino, or monovalent or polyvalent cation; and

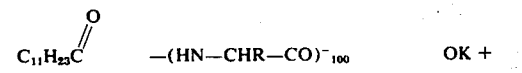
d. mixtures thereof, the scleroprotein derivative being dissolved in the nail varnish in the absence of water.

2. The nitrocellulose varnish according to claim **1** wherein said ester included in the varnish is:



wherein:
R is a protein hydrolysate with the following contents of amino acids (average percent by weight of protein): Lysine 5; Histidine 1; Arginine 7; Aspartic acid 5; Threonine 2; Serine 3; Glutamic acid 11; Proline 11 Glycine 17; Alanine 8; Valine 2; Methionine 2; Isoleucine 3; Leucine 3; Thyrosine 2; 10 2; Hydroxylysine 2; Hydroxyproline 15.

3. The nitrocellulose nail varnish according to claim **1** wherein said protein fatty acid condensate included in the varnish is:



wherein:
R is a protein hydrolysate with the following contents of amino acids (average percent by weight of protein): Lysine 5; Histidine 1; Arginine 7; Aspartic acid 5; Threonine 2; Serine 3; Glutamic acid 11; Proline 10; Blycine 17; Alanine 8; Valine 2; Methionine 2; Isoleucine 3; Leucine 3; Thyrosine 2; Phenylalanine 2; Hydroxylysine 2; Hydroxyproline 15.

4. The nitrocellulose nail varnish according to claim **1** wherein the base of said nail varnish exclusive of said scleroprotein derivative comprises by weight about 17.5 per cent nitrocellulose containing about 18 per cent by weight dibutyl phthalate; about 2.9 per cent dibutyl phthalate; about 12.6 per cent aryl sulfonamideformaldehyde resin; about 3.4 per cent camphor; about 26.6 per cent ethyl acetate; about 23.0 per cent butyl acetate; and about 14.0 per cent toluol.

5. The nitrocellulose nail varnish according to claim **1** which contains as the collagen hydrolysate from about 0.05 to 1.8 percent by weight soluble embryonic calfskin protein.

6. The nitrocellulose nail varnish according to claim **1** which contains as the alcoholic ester an ethyl ester of a hydrolyzed collagen-derived polypeptide.

7. The nitrocellulose nail varnish according to claim **1** which contains as the fatty acid condensate a liquid detergent condensation product of a proteinhydrolysate with acyl halides of plant oleic or coconut fatty acids which is neutralized with potassium hydroxide.

8. The nitrocellulose nail varnish according to claim **1** which contains as the fatty acid condensate a liquid detergent condensation product of a proteinhydrolysate with acyl halides of plant oleic or coconut fatty acids neutralized with triethanol amine.

9. The nitrocellulose nail varnish according to claim **1** which contains as the fatty acid condensate a mixture which comprises about 60 percent lauric diethanolamide and about 30 percent of a liquid condensation product of protein hydrolysates with acyl halides of

plant oleic or coconut fatty acids which is neutralized with triethanol amine.

10. The nitrocellulose nail varnish according to claim **4** which comprises by weight exclusive of said scleroprotein derivative, about 77 percent of said varnish base, about 3 percent colored dye solution; about 3.5 percent ethyl acetate; and about 16.5 percent iridescent shining pigment.

11. The nitrocellulose nail varnish according to claim **10** which contains as the scleroprotein derivative collagen hydrolysate from about 0.05 to 1.8 percent by weight soluble embryonic calfskin protein.

12. The nitrocellulose nail varnish according to claim **10** which contains as the scleroprotein derivative from about 0.05 to 5 percent by weight of an ethyl ester of a hydrolyzed collagen-derived polypeptide.

13. The nitrocellulose nail varnish according to claim **10** which contains as the scleroprotein derivative from about 0.05 to 4 percent by weight of a liquid condensation product of a protein-hydrolysate with acyl halides of plant oleic or coconut fatty acids which is neutralized with potassium hydroxide.

14. The nitrocellulose nail varnish according to claim **10** which contains as the scleroprotein derivative from about 0.05 to 0.9 percent by weight of a liquid condensation product of a protein-hydrolysate with acyl halides of plant oleic or coconut fatty acids neutralized with triethanol amine.

15. The nitrocellulose nail varnish according to claim **10** which contains as the scleroprotein derivative from about 0.05 to 4 percent by weight of a mixture which comprises about 60 percent lauric diethanolamide and about 30 percent of a liquid condensation product of protein hydrolysates with acyl halides of plant oleic or coconut fatty acids which is neutralized with triethanol amine.

16. The nitrocellulose nail varnish according to claim **4** which comprises by weight, exclusive of said scleroprotein derivative about 80 percent of said varnish base, about 17 percent colored dye solution; and about 3 percent ethyl acetate.

17. The nitrocellulose nail varnish according to claim **16** which contains as the scleroprotein derivative collagen hydrolysate from about 0.05 to 1.8 percent by weight soluble embryonic calfskin protein.

18. The nitrocellulose nail varnish according to claim **16** which contains as the scleroprotein derivative from about 0.05 to 5 percent by weight of an ethyl ester of a hydrolyzed collagen-derived polypeptide.

19. The nitrocellulose nail varnish according to claim **16** which contains as the scleroprotein derivative from about 0.05 to 4 percent by weight of a liquid condensation product of a protein hydrolysate with acyl halides of plant oleic of coconut fatty acids which is neutralized with potassium hydroxide.

20. The nitrocellulose nail varnish according to claim **16** which contains as the scleroprotein derivative from about 0.05 to 0.9 percent by weight of a liquid condensation product of a protein-hydrolysate with acyl halides of plant oleic or coconut fatty acids neutralized with triethanol amine.

21. The nitrocellulose nail varnish according to claim **16** which contains as the scleroprotein derivative from about 0.05 to 4 percent by weight of a mixture which comprises about 60 percent lauric diethanolamide and about 30 percent of a liquid condensation product of protein hydrolysates with acyl halides of plant oleic or coconut fatty acids which is neutralized with triethanol amine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 3 907 580

DATED : September 23, 1975

INVENTOR(S) : Goswin Clemens van Ham

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 8, Line 17:

"Proline 11" should be --- Proline 10 ---.

Column 8, Line 18:

"10 2" should be --- Phenylalanine 2 ---.

Signed and Sealed this

Thirteenth Day of July 1976

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks