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(54) Title: HAIR CARE COMPOSITIONS COMPRISING BIS - PANTOYL - CYSTAMINE OR A DERIVATIVE THEREOF

(57) Abstract: The invention relates to novel hair care compositions comprising bis-pantoyl-cystamine or a derivative thereof.

HAIR CARE COMPOSITIONS COMPRISING BIS-PANTOYL-CYSTAMINE OR A DERIVATIVE THEREOF

The present invention relates to novel hair care compositions and to a novel use of bis-pantoyl-cystamine or a derivative thereof in hair care compositions.

In accordance with the present invention it has been found that the treatment of hair with hair care compositions containing bis-pantoyl-cystamine or a derivative thereof results in strengthening the hair. Thus, the present invention, in one aspect, relates to novel hair care compositions comprising bis-pantoyl-cystamine or a derivative thereof. In another aspect the invention relates to a method of strengthening hair by treatment of hair with an effective amount of bis-pantoyl-cystamine or a derivative thereof. In yet another aspect, the invention relates to the use of bis-pantoyl-cystamine or a derivative thereof in the manufacture of hair care compositions for strengthening hair. Finally, the invention is concerned with certain novel isomers of bis-pantoyl-cystamine and mixtures thereof, as well as derivatives of these novel isomers and isomeric mixtures.

Hair is often exposed to harsh conditions such as sun, heat, and chemical damage, eg from detergents, bleaching, dyeing, straightening or permanent waving. Such conditions generally result in damage to the hair, disrupting the organized structure of interwoven keratinous fibers. The longer the hair grows from the root, the more severe can the cumulative effects of this history of damage become. One consequence of such damage is loss of tensile strength, which can lead to breakage of hair and hair loss.

Hair fiber is comprised of four structural units: cuticle, cortex, medulla, and intercellular cement (C. R. Robbins, Chemical and Physical Behavior of Human Hair, 3rd Edition, Springer-Verlag, 1994 .) The mechanical properties of the hair are primarily determined by the cortex, which is approxiamtely 75 to 90 % of the hair bulk. The cortex is comprised of macrofibrils of cells aligned along the fiber axis. These macrofibrils are in turn are composed of protein microfibrils comprised of coiled protein molecules arranged in a highly organized manner and embedded in an amorphous protein matrix of intercellular cement. The water-penetrable cement binds the microfibrils together and is the major pathway for diffusion into the fibers. It is the primary protein structure of the cortex that is sensitive to damage which leads to loss of hair properties such as strength. Thus there is a need for substances which can protect the keratinous proteins from harsh conditions and to help restore the structure following damage by harsh conditions.

A traditional hair treatment has been use of mildly acidic substances such as acetic or citric acids, or more recently ascorbic acid which shrink and harden the cortex, sometimes as part of a neutralizing rinse after an akaline treatment. Alternatively treatment can be made with lacquers, gums, or resins sprayed or applied to the hair. However such treatments can make hair stiffen and become brittle and subject to breakage. The use of synthetic and natural polymers, protein hydrolyzates etc. in hair care formulations, such as sprays, mousses, gels, shampoos and conditioners is common in hair care. Such products deposit polymers onto hair, altering surface properties, imparting benefits such as conditioning, ease of styling, shine, and elasticity. However the polymers are generally deposited by physical adsorption onto the hair surface and are removable by washing therefore the benefits are only temporary. An alternative approach is the introduction of polymers inside the hair. Since high molecular weight polymers are too large to diffuse into the hair strands, the treatment of hair with monomers and subsequent polymerization has been proposed. However since the monomers are often toxic and allergenic materials, this approach is a laboratory curiosity and has no commercial significance.

The compound bis-pantoyl-cystamine, (by systematical name : N,N'-(dithio-2,1-ethanediyl)bis(2,4-dihydrox-3,3-dimethyl) butanamide) which has the formula

$$(HO\text{-}CH_2\text{-}C(CH_3)_2\text{-}C^*HOH\text{-}CO\text{-}NH\text{-}CH_2CH_2\text{-}S\text{-})_2$$

contains two chiral centers as indicated by an asterisk. Therefore, bis-pantoyl-cystamine may exist in 3 isomeric forms with RR, RS and SS configurations. The isomer with RR configuration is known and has been described in the literature (Boxer at al, J. Biol Chem., 1955, 217,541 Shimizu et al Chem Pharm Bull, 1970, 18, 838 .) The RR/SS diastereomeric pair and the RS (meso) isomer, and mixtures of RR, SS, RR/SS and RS are new and, as such, are also an object of the present invention. While all isomeric forms and their mixtures are intended for use in accordance with the invention, the new isomers and mixtures are preferred. Particularly preferred are the RR/SS diastereomeric pair, and the mixture composed of RR, RS, and SS isomers in a molar ratio of about 25:50:25 to about 30:40:30. They possess unexpected advantageous properties for manufacture, handling, and use in hair care.

The substances described are conveniently prepared by reaction of pantolactone with cystamine. When R-pantolactone is used, the RR isomer results which in pure form is found to be a very viscous oil. When S-pantolactone is used, the SS isomer results, which as the pure isomer is also a very viscous oil. These materials are somewhat difficult to handle due to their high viscosity even when warmed. Purification of such materials is normally more difficult than with crystalline solids.

When equal amounts of the RR and SS isomers are mixed there results a new substance, an RR/SS diasteromeric pair , which is a solid easily purified by crystallization.

When racemic pantolactone is used, there results a mixture composed of

RR, RS, and SS isomers in a molar ratio of 25:50:25. Unexpectedly, this mixture can easily be crystallized to a white solid which can be further purified by recrystallization, e.g., from ethyl acetate or water. Such purification may result in a change of the RR, RS, and SS isomer molar ratio to about 30:40:30. For the purposes of the present invention, the preferred molar ratio in terms of the RS (meso) to RR/SS ratio is in the range from about 50:50 to about 30:70.

Cosmetic products require the highest standard of purity and safety because of contact to human skin, hair, and mucous membranes. Customers are particularly sensitive to color and odor of such products. Thus purification to the highest quality of this type products is

essential. And ease of purification an advantage to manufacturing. Thus the RR or SS isomers can be used as hair care products provided specialized methods of purification are employed. The mixture of RR/SS and RS meso isomers offer an advantage is being easily purified by conventional chemical process techniques such as crystallization. Accordingly, for the purposes of the present invention the use of the mixture of RR/SS and RS meso isomers, and derivatives thereof, is preferred.

The term "derivative" as used herein denotes any compound that is obtained from bis-pantoyl-cystamine by modification of the hydroxy groups contained therein, particularly the terminal hydroxy groups, and which exert a similar activity as bis-pantoyl-cystamine. Examples of such derivatives are acylates, particularly acylates formed with aliphatic, aromatic or araliphatic carboxylic acids containing 2-20 carbon atoms, which may be saturated or unsaturated, and may be substituted by, e.g. hydroxy groups, such as the mono- or di-acetate, propionate, butyrate, caproate, caprylate, caprate, laurate, myristate, lactate, 2-hydroxycaprylate, 2-hydroxycaprate, 2-hydroxylaurate, 2-hydroxymyristate, di-2-heptyl-undecanoate, and salicylate. Examples of acylates derived from unsaturated carboxylic acids are oleates and linoleates.

The term " hair care composition" as used herein denotes any conventional hair care product, such as shampoos, conditioners, tonics, styling gels, mousses, hair sprays, pomades, setting lotions, colouring and permanent waving compositions. Of particular interest for the purpose of the present invention are shampoos, tonics and conditioners.

Bis-pantoyl-cystamine and derivatives thereof as defined above show good performance in hair treatment formulations, strenthening of hair and making it easier to comb. Further the use of these substances shows cumulative improvement of hair strenght with repeated use. It has been found that the product accumulates within the hair after repeated application from hair care products.

The amount of bis-pantoyl-cystamine or derivative thereof in hair care compositions in accordance with the present invention is suitably in the range from about 0.1 wt.-% to about 10 wt.-%, preferably from about 0.5 wt.-% to about 5 wt.-%, and most preferably from about 0.5 wt.-% to about 2 wt.-%. The bis-pantoyl-cystamine or derivative thereof may be incorporated in such formulations by adding to the final formulation or at any appropriate intermediate step in the manufacture of said formulations.

The hair care compositions of the present invention, besides comprising bis-pantoyl-cystamine, may contain ingredients which are conventionally used in hair care compositions such as disclosed in general terms in Ullmann's Encyclopedia of Industrial Chemistry (1989), Vol A 12, Hair Preparations, and more specifically, e.g., in International Patent Application No. WO 00/06094, WO 00/07550 and WO 01/06994, the contents of which are incorporated herein for reference.

Thus, hair shampoos contain at least one surfactant suitable for cleaning hair, such as for example, the shampoo compositions set forth in the examples below. The base ingredient of a shampoo composition is a water/anionic surfactant system that emulsifies the accumulated surface oils and removes them during the rinsing process. Suitable anionic surfactants are C_{10-18} -alkyl ether sulfates, C_{10-18} -alkyl sulfates, sulfuric acid fatty alcohol esters and salts thereof like e.g. ammonium, sodium, potassium or mono-, di-or triethanolamine salts. Examples of C_{10-18} -alkyl ether sulfates are sodium lauryl ether sulfate, potassium lauryl ether sulfate, ammonium lauryl ether sulfate. Examples of C_{10-18} -alkyl sulfates are sodium lauryl sulfate (Sodium Laureth Sulfate), potassium lauryl sulfate and ammonium lauryl sulfate. Sodium Laureth Sulfate is available from Henkel under the tradename TEXAPON. Still further suitable anionic surfactants include α-olefin sulfonates, alkyl monoglyceride sulfonates, alkyl benzene sulfonates, alkyl sarcosinates,

alkyl monoglyceride sulfates, monoalkylether sulfosuccinates, alkyl ether carboxylates and the like. The anionic surfactant can be employed at concentrations within the range from about 5 to about 40 wt%, preferably about 15 wt%.

Hair conditioners are used to restore the original condition of hair. Such conditioners include, for example, silicones, cationic surfactants and quaternary ammonium compounds, and synthetic cationic polymers. Other components for use in hair care compositions in accordance with the present invention include moisturizing agents, thickeners or viscosity modifying agents for enhancing hand application, lathering agents for increasing foaming, foam stabilizers, and pearlizing agents. Examples of yet other components which are commonly included in hair care compositions are perfumes, pH control agents, colorants, preservatives, and antimicrobials.

The hair care compositions of the present invention may contain further ingredients to protect the hair against detrimental environmental impact and to improve the health of the hair.

Such ingredients may be one or more agents selected from UV screening agents, vitamin A or derivatives thereof, Vitamin C or derivatives thereof, vitamin E or derivatives thereof, a vitamin from the B complex, panthenol, phytantriol or derivatives thereof.

The term "UV screening agent" means a compound or composition that absorbs UV radiation in the range of about 320 nm to about 400 nm (UV-A) or in the range of about 280 nm to about 320 nm (UV-B). Such UV filters include, for example, dibenzoylmethane derivatives such as butyl methoxydibenzoylmethane (PARSOL 1789), benzylidene-cyanoacetates such as 4-methoxy-benzylidene-cyanoacetic acid n-hexyl ester, triazine derivatives such as 4,4'-(6-(bis(2-ethyl-hexyl)-amino)-s-triazine-2,4-diyl)-diresorcinol, anilinomethylene derivatives such as 2-(4-ethoxy-anilinomethylene)-propanedioic acid diethyl ester, camphor derivatives sich as 4-methyl benzylidene camphor (PARSOL 5000) and terephtalylidene-3,3'-dicamphor-10,10'-disulfonic acid, benzimidazol derivatives such as 2,2'-(1,4-phenylen)-bis-1H-benzimidazol-4,6-disulfonic acid Na salt; cinnamates such as octyl methoxycinnamate (PARSOL MCX); salicylic acid derivatives such as octyl salicylate and homomenthyl salicylate; p-aminobenzoic acid derivatives such as p-dimethylaminobenzoic acid 2-ethylhexyl ester; benzophenone derivatives such as 2-hydroxy-4-methoxy-benzophenone, and 4-phenyl-benzophenone-2-carboxylic acid 2-ethylhexyl ester; anthranilates such as homomenthyl-N-acetylanthranilate and menthylanthranilate; acrylates such as 2-ethylhexyl-2-cyano-3,3-diphenylacrylate ((PARSOL 340); benzimidazole derivatives such 2-phenylbenzimidazole-5-sulphonic acid (PARSOL HS); benzoxazole derivatives such as 2-phenyl-5-methyl-benzoxazole, malonate derivatives such as dimethico diethylbenzalmalonate (PARSOL SLX); triazine derivatives such as 2,4-Bis((4-(ethyl-hexylox)-2-hydroxy)-phenyl)-6-(4-methoxyphenyl)-1,3,5-triazine (Tinosorb S - Ciba); bezotriazol derivatives such as 2,2'-Methylene-bis-(6(2H-benzotriazol-2-yl)-4-(1,1,3,3,-tetramethylbutyl)phenol) (Tinosorb M - Ciba), Uvinul T-150 (BASF), UVASORB HEB (3V-Sigma). In preferred compositions the UV-A filter is selected from the group consisting of PARSOL 1789, 4,4'-(6-(bis(2-ethyl-hexyl)-amino)-s-triazine-2,4-diyl)-diresorcinol (Triazin), 2-(4-ethoxy-anilinomethylene)-propanedioic acid diethyl ester, and mixtures thereof, PARSOL MCX or PARSOL SLX. The sunscreens agents may be present in the hair care compositions in an amount from about 0.01 wt.-% to about 5.0 wt.-%.

A vitamin A derivative for use in the present invention is, e.g. a fatty acid ester such as vitamin A acetate or palmitate which may be present in the hair care products in an amount from about 0.01 wt.-% to about 1.00 wt.-%. A vitamin E derivative for use in the present invention is, e.g. tocopheryl acetate. Tocopheryl acetate may be present in the hair care products in an amount from about 0.05 wt.-% to about 5 wt.-%. Examples of

vitamins from the B complex for use in the present invention are vitamin B_3, B_6 and biotin. Vitamin B_3 may be present in the hair care products in an amount from about 0.01 wt.-% to about 1.00 wt.-%. Vitamin B_6 may be present in the hair care products in an amount from about 0.01 wt-% to about 1.00 wt.-%. Biotin may be present in the hair care products in an amount from about 0.001wt.-% to about 0.5 wt.-%. Panthenol may be present in the hair care products in an amount from about 0.05 wt.-% to about 5.00 wt.-%. Phytantriol may be present in the hair care products in an amount from about 0.01 wt.-% to about 2.5 wt.-%. Sodium Ascorbyl Phosphate may be present in the hair care products in an amount from about 0.05 wt.-% to about 5.00 wt.-%.

In a preferred aspect of the present invention, bis-pantoyl-cystamine and derivatives thereof, particularly RR/SS bis-pantoyl-cystamine, i.e. the diastereomeric pair, as well as the mixture composed of RR, RS and SS isomers of bis-pantoyl-cystamine in a ratio of about 25:50:25 are used in combination with panthenol and/or phytantriol. Addition of phytantriol to bis-pantoyl-cystamine or bis-pantoyl-cystamine/panthenol hair care formulations results in a significant synergistic increase in tenacity of the hair treated with such formulations. Most preferred is a mixture of RR/SS bis-pantoyl-cystamine, as well as the mixture composed of RR, RS and SS isomers of bis-pantoyl-cystamine, with phytantriol.

The following Examples illustrate the invention further.

Example 1

Preparation of RR-bis-pantoyl-cystamine

36.8 g of R-pantolactone was melted in a 500 mL round bottom flask at 95 °C inner temperature using an oil bath. To the stirred colorless liquid there was added dropwise 21.2 g of cystamin base and 0.94 ml of butanol . After 24 hours of heating the brown sirupy solution was allowed to cool to below 80 °C, then 225 ml of ethylacetate was added dropwise over 20 min. After the addition of 0.6 g of activated charcaol the hot suspension filtered over diatomaceous earth and filter paper. The light yellow clear solution was allowed to cool over the course of 2 hours during which time an oil settled out. The solvent was removed by rotovacuum distillation at 75 °C and 40 mm to yield a yellowish brown oil of 32.0 g crude product. This was chromatographed on 500 g of silica gel using a 9:2 mixture of ethylacetate and ethanol The homogeneous fractions were evaporated, then dried by heating in vacuo at 70 °C and 0.25 mm for 40 hours to yield 18.4 g of RR-bis-pantoyl-cystamine as a glassy orange-coloured oil. HPLC analysis showed a purity of 95% with a diastereomer ratio of 3:96 of RS meso and RR/SS isomers. (The small amount of products of the S isomer results from S isomer in the R-pantolactone.) This sample remained a glass on storage at room temperature for over 2 months. NMR data were consistent with the structure assigned.

Example 2

Preparation of SS-bis-pantoyl-cystamine

2 g of S-pantolactone was melted at 95 C internal temperature in a round bottom flask

1.16 gof cystamin base was added dropwise followed by 0.05 ml of butanol and the mixture was stirred for 22 hours. The were added to the brown sirupy mixture

12 ml of ethyl acetate and 0. 03 g of activated charcoal, the mixture filtered through diatomaceous earth and paper, and the filtrate evaporated in vacuo. The resulting yellow oil was chromatographed on silica and the recovered product dried by heating at 70 °C at 0.25mm to constant weight. There was obtained 0.74 g of orange glass comprised of 94 % of SS-bis-pantoyl-cystamine along with 2 % of its RS meso isomer (by HPLC analysis). This substance did not crystallize on storage at room temperature for 2 months.

Example 3

Preparation of the RR/SS bis-pantoyl-cystamine (enantiomeric pair)
208 mg of the RR isomer and 208 mg of the SS isomer were mixed and kept at room temperature under argon overnight during which the mixture crystallized. 170 mg of the mixture was recrystallized from 8 mL of methanol-ethyl acetate (3:5) to give 134 mg of beige crystals of RR/SS bis-pantoyl-cystamine (enantiomeric pair)
melting point ca. 145 °C.

Example 4

Preparation of mixture of RR/SS- and RS-bis-pantoyl-cystamine.
121.5 g of DL-pantolactone was melted in a 2.5 L round bottom flask at an inner temperature of 95 °C. To this there was added dropwise 73.7 of cystamin base and 1.0 g of n-butanol. The mixture was stirred and heated for 16 hours, then the resulting sirupy brown solution was cooled to below 80 °C and was added over 20 minutes 744 ml of ethyl acetate and 2.0 g of activated charcoal, then the mixture was filtered over a teflon membrane filter. The clear filtrate was allowed to cool over the course of 2 hours to room temperature during which at about 50 °C crystallization occurred. The mixture was allowed to stir at room temperature for 3 hours, cooled to 10°C, held for 30 minutes, then filtered, and the solids rinsed with 150 mlof ethyl acetate (10 °C) After 12 hours drying at 50 °C at 4mm there were obtained 165.8 g of beige solids consisting of 96 % by weight of a mixture of diastereomers of bis-pantoyl-cystamine. HPLC analysis showed this to be composed of a mixture of 41 % RS- isomer with 56% of the RR/SS-enantiomeric pair.

Example 5

Shampoo with 2% Bis-pantoyl-cystamine (a rinse-off formulation)

	Ingredients	% (w/w)
A)	Texapon NSO (Sodium Laureth Sulfate)	50.00
	Cetiol HE (PEG-7 Glyceryl Cocoate)	3.00
	Dehyton K (Cocamidopropyl Betaine)	5.00
	Preservative	q.s.
	Deionized Water	35.60
	Sodium Chloride	2.00

	EDETA BD (Disodium EDTA)	0.20
	D-Panthenol	0.20
	Bis-pantoyl-cystamine (diastereomeric mixture of Example 4)	2.00
	Crothix LVR (PEG-150 Pentaerythrityl Tetrastearate & Polysorbate 20 & PEG-7 Glyceryl Cocoate)	2.00
B)	KOH 10%	q.s.
		100.00

Procedure:

Part A: Add the ingredients and heat to 40°c under slow agitation until a clear foam-free mixture is obtained. Add Part B to adjust the pH to 6.5

Example 6

Hair Tonic with 0.5% Bis-pantoyl-cystamine (a leave-on formulation)

	Ingredients	% (w/w)
A)	Water	Ad. 100
	Glycerin	2.00
	Sodium PCA	2.00
	Preservative	q.s.
	Bis-pantoyl-cystamine (diastereomeric mixture of Example 4)	0.50
	D-Panthenol	0.20
B)	Citric acid (10%)	q.s.

Procedure:

Part A: Add all the ingredients under agitation at room temperature until a clear solution is obtained. Adjust final pH to 6.0 with part B.

Example 7

Multi Vitamin Protective Hair Tonic with 1.0% Bis-pantoyl-cystamine (a leave-on formulation)

	Ingredients	% (w/w)
A)	Water	Ad. 100
	Glycerin	2.00
	Sodium PCA	2.00
	Preservative	q.s.
	Bis-pantoyl-cystamine (diastereomeric mixture of Example 4)	1.00
	Niacinamide (Vitamin PP)	0.10
	Biotin (Vitamin H)	0.01
	Sodium Ascorbyl Phosphate	0.20
	Sodium PCA	2.00
	D-Panthenol	0.20
B)	Cremophor RH-40 (PEG-40 Hydrogenated Castor Oil)	5.00
	Vitamin A Palmitate (1.7 M.I.U./G)	0.10
	Vitamin E Acetate	0.20
	Phytantriol	0.20
	PARSOL MCX	1.00
	PARSOL SLX	0.50
	PARSOL 1789	0.20
C)	Citric acid (10%)	q.s.

Procedure:

Part A: Add all the ingredients under agitation at room temperature until a clear solution is obtained. Add part B. Adjust final pH to 7.0 with part C.

Example 8

The hair strengthening effect of bis-pantoyl-cystamine from a shampoo and conditioner was determined. The formulations tested were the following:

Shampoo :

Ingredients	A	B	C
Bis-pantoyl-cystamine as obtained in Example 4	1 wt.%	0.5 wt.%	none
Texapon NSO (Sodium Laureth Sulfate)	30 wt.%	30 wt.%	30 wt.%
Monamid 716 (Lauramide DEA)	3 wt.%	3 wt.%	3 wt.%
Sodium Chloride	1 wt.%	1 wt.%	1 wt.%
Citric Acid, 50 %	0.1 wt.%	0.1 wt.%	0.1 wt.%
Preservative	q.s.	q.s.	q.s.
Deionized Water	Ad. 100	Ad. 100	Ad. 100

Hair Conditioner :

Ingredients	D	E	F
Bis-pantoyl-cystamine as obtained in Example 4	1 wt.%	0.5 wt.%	none
Propylene Glycol	5 wt.%	5 wt.%	5 wt.%
Lanette 16 (Cetyl Alcohol)	2.5 wt.%	2.5 wt.%	2.5 wt.%
Ammonyx 4002 (Steralkonium Chloride)	1 wt.%	1 wt.%	1 wt.%
Preservative	q.s.	q.s.	q.s.
Deionized Water	90.45wt.%	90.95 wt.%	91.45 wt.%

PROCEDURE:

Sample Preparation

Hair samples (Virgin hair and Bleached hair) of approximately 20 cm in length were used. Prior to experimentation, these hairs were stored at constant temperature (20°C) and relative humidity (15% RH).

Hair Strength Measurement

There are a number of experimental methods used to assess the strength of hair and changes therein as a result of treatments. Commonly used is a mechanical tensile tester, such as supplied by Instron Corporation, wherein hairs are forceably pulled at a measured rate and their elongation measured. Practically speaking the Hookean and yield regions are of most relevance to the daily life of human beings, since it is desireable to not damage hair. However the most common expression of hair strength is tenacity, which is defined as the ratio of breaking force to linear density of the hair, and is determined from the force required to break a multiple number of hairs. Comparison of tenacity measurements is the used to estimate the degree of effectiveness of a treatment in strengthening the hair. Necessary is to compare tenacity measurements under identical conditions of hair treatment and humidity, changing only the test material within the formulation. It is well known that the elastic limits of hair depend on the nature of the hair (such as hair color), the treatment history of the hair (so called "virgin" vs "normal" vs "damaged ") , and the moisture content of the hair. So called "normal" dry hair can have a moisture content of 5-10 % and a limit of elasticity of 20-30%, beyond which there results damage to the hair whereas wet hair can contain as much as 30 % moisture and have an elastic limit of ca 60 %.

Hair, upon extension with increasing forces, passes through three phases. The first phase (the elastic region) is characterized by reversible extension. The second phase is the yield region, characterized by an irreversible transformation in which covalent bonds are probably broken. Finally, the third phase corresponds to the breaking point, where complete fiber breakage occurs. Research in several laboratories has previously shown that the breaking point of hair closely related to hair diameter, and may not necessarily be an indication of overall hair damage. Thus, the yield region is the one most likely to correlate with covalent and disulfide bond breakage in hair, (i.e., overall hair damage), and therefore, evaluating the yield slope can provide a measurement of hair damage.

A custom designed tensile strength tester was used to asses the stress-strain behavior of hair. For this, a single strand of hair of 20 cm long was extended with a force at 20 g load setting at a speed of 100 mm/minute. The slope of the yield region which correlates with covalent and disulfide bond breakage (i.e., overall hair damage) was measured for each hair.

For each control or treatment group, 10 strands of hair were mesured and the mean yield slope was calculated and used to reflect the extent of hair damage.

Product Treatment

For Shampoo and conditioner treatments, the virgin and bleached hairs were treated by applying approximately 2 ml of the test shampoo or conditioner to approximately 6 gm of wet hair. The test shampoo or conditioner was applied evenly with continuous massage and was allowed to leave on hair for 1 minute. Then the hair swatch was rinsed off thoroughly with running luke warm water for 20 seconds. The hair was then squeezed dry with paper towel and then air dried prior to hair strength measurements.

Effects of Shampoo Treatments

The mean yield slope values for the untreated virgin and bleached hair; as well as the hair treated by the various test shampoos and conditioners are summarized in Table 1, 2, 3 and 4.

TABLE 1

Hair tensile strength (g/mm) of virgin hair often treatment with shampoo A, B and C

Hair Sample	Untreated	A		B		C	
		1 cycle	5 cycle	1 cycle	5 cycle	1 cycle	5 cycle
1	0.610	0.704	0.719	0.567	0.622	0.608	0.628
2	0.583	0.681	0.722	0.608	0.645	0.592	0.596
3	0.562	0.608	0.587	0.682	0.597	0.574	0.594
4	0.533	0.561	0.671	0.591	0.611	0.613	0.618
5	0.587	0.633	0.642	0.584	0.593	0.626	0.632
6	0.569	0.572	0.790	0.632	0.638	0.581	0.588
7	0.604	0.717	0.783	0.601	0.656	0.587	0.676
8	0.592	0.765	0.656	0.617	0.678	0.625	0.654
9	0.566	0.638	0.692	0.586	0.701	0.611	0.641
10	0.547	0.647	0.741	0.604	0.641	0.606	0.603
Average	0.575	0.653	0.700	0.607	0.638	0.602	0.623
S.D.	0.024	0.065	0.064	0.032	0.034	0.018	0.029
t*		-4.990	-6.238	-2.236	-5.100	-2.884	-5.764
p*		0.0007	0.0002	0.05<p<0.1	0.0006	0.01<p<0.05	0.0003
%Change in Tensile Strength		13.44%	21.73%	5.54%	10.93%	4.69%	8.29%

* Paired T Test at 95% confidence limited

TABLE 2

Hair tensile strength (g/mm) of virgin hair often treatment with conditioner D, E and F

Hair Sample	Untreated	D		E		F	
		1 cycle	5 cycle	1 cycle	5 cycle	1 cycle	5 cycle
1	0.610	0.769	0.724	0.692	0.693	0.661	0.604
2	0.583	0.725	0.736	0.671	0.688	0.592	0.637
3	0.562	0.690	0.851	0.765	0.711	0.611	0.716
4	0.533	0.832	0.830	0.704	0.683	0.642	0.723
5	0.587	0.787	0.814	0.711	0.656	0.608	0.748
6	0.569	0.762	0.769	0.702	0.717	0.682	0.706
7	0.604	0.747	0.773	0.655	0.728	0.645	0.654
8	0.592	0.783	0.792	0.642	0.689	0.701	0.681
9	0.566	0.726	0.788	0.603	0.728	0.622	0.627
10	0.547	0.781	0.811	0.781	0.737	0.680	0.646
Average	0.575	0.760	0.789	0.693	0.703	0.644	0.674
S.D.	0.024	0.040	0.040	0.054	0.025	0.036	0.048
t*		-11.350	-11.433	-5.455	-10.491	-5.056	-5.119
P*		<0.0001	<0.0001	0.0004	<0.0001	0.0007	0.0006
%Change in Tensile Strength		32.14%	37.11%	20.39%	22.20%	12.01%	17.19%

* Paired T Test at 95% confidence limited

TABLE 3

Hair tensile strength (g/mm) of bleached hair often treatment with shampoo A, B and C

Hair Sample	Untreated	A		B		C	
		1 cycle	5 cycle	1 cycle	5 cycle	1 cycle	5 cycle
1	0.360	0.412	0.433	0.398	0.411	0.387	0.407
2	0.382	0.487	0.513	0.427	0.438	0.352	0.381
3	0.441	0.466	0.508	0.420	0.443	0.377	0.392
4	0.402	0.481	0.516	0.418	0.440	0.418	0.433
5	0.413	0.493	0.522	0.436	0.471	0.403	0.418
6	0.411	0.447	0.496	0.447	0.460	0.381	0.409
7	0.357	0.469	0.501	0.408	0.438	0.427	0.436
8	0.394	0.436	0.489	0.384	0.407	0.440	0.471
9	0.385	0.427	0.466	0.411	0.433	0.416	0.432
10	0.401	0.489	0.532	0.430	0.477	0.435	0.455
Average	0.395	0.461	0.498	0.418	0.442	0.404	0.423
S.D.	0.025	0.029	0.029	0.019	0.023	0.029	0.028
t*		-6.836	-12.144	-3.197	-6.048	-0.690	-2.261
p*		<0.0001	<0.0001	0.01<p<0.05		p>0.4	0.05<p<0.1
%Change in Tensile Strength		16.75%	26.10%	5.90%	11.96%	2.28%	7.30%

* Paired T Test at 95% confidence limited

TABLE 4

Hair tensile strength (gm/mm) of bleached hair often treatment with conditioner D, E. and F

Hair Sample	Untreated	D		E		F	
		1 cycle	5 cycle	1 cycle	5 cycle	1 cycle	5 cycle
1	0.360	0.536	0.551	0.476	0.494	0.423	0.473
2	0.382	0.497	0.521	0.517	0.524	0.418	0.437
3	0.441	0.504	0.518	0.461	0.483	0.452	0.461
4	0.402	0.531	0.547	0.485	0.489	0.437	0.457
5	0.413	0.506	0.532	0.454	0.473	0.443	0.487
6	0.411	0.488	0.508	0.501	0.518	0.445	0.495
7	0.357	0.473	0.493	0.441	0.459	0.417	0.436
8	0.394	0.492	0.518	0.407	0.461	0.442	0.453
9	0.385	0.466	0.523	0.412	0.456	0.436	0.445
10	0.401	0.553	0.603	0.428	0.459	0.434	0.438
Average	0.395	0.505	0.531	0.458	0.482	0.435	0.458
S.D.	0.025	0.028	0.030	0.037	0.025	0.012	0.021
t*		-9.899	-11.425	-4.630	-8.209	-8.146	-7.794
p*		<0.0001	<0.0001	0.001<p<0.05	<0.0001	<0.0001	<0.0001
%Change in Tensile Strength		27.88%	34.67%	16.12%	22.05%	10.16%	16.12%

* Paired T Test at 95% confidence limited

The above results demonstrate that the damage (bleached) hair showed a much lower yield slope than virgin hair which is indicative of greater hair damage (0.395 vs. 0.575).

For the effects of shampoo treatments on virgin (undamaged) hair, Test Shampoo A was shown to provide the greatest increase in hair strength, followed by Test Shampoos B then C. As expected, multiple treatment (5 cycles) resulted in much more improvement than a single treatment.

For the conditioner; the effects of the various test conditioner treatments are more profound, with much better hair strength improvement seen than the shampoo treatments. The order of activity of the conditioner treatments on virgin hair was found to be Test Conditioner D > E > F.

For the damage hair, the results observed are quire similar to those found for virgin hair; with Test Shampoo A and Conditioner D being the most efficacious. The order of activity for the various shampoo and conditioner treatments is the same at those observed for virgin hair.

Example 9

In a further test run, the efficacy of shampoos containing bis-pantoyl-cystamine and phytantriol for improving the tensile strength of human hair was determined. In this test run, the breaking force and breaking elongation were measured ten times on a harp of 10 hairs using an INSTRON 5543 apparatus. The samples were sprayed with water and stretched with a speed of 10 mm/min until all ten hairs were broken. The hair fragments were collected, dried and weighed. The tenacity of the hair was calculated from the breaking force (cN) divided by the linear density (mg/m) of the hair fibers. A typical tenacity of European hair is about 14 cN·m/mg.

For the test, blond Caucasian virgin untreated hair was used. The hair was washed with a shampoo formulation as indicated below:

Shampoo formulation :

Ingredient	Concentration % w/w
Texapon N (Sodium Laureth Sulfate)	9
Dehyton G (Disodium Cocoamphodiacetate)	5
Tego Betaine L7 (Cocamidopropyl Betaine)	5
Tween 20	0.5
Bis-pantoyl-cystamine	q.s.
Phytantriol	q.s.
Deionized Water	ad 100

The tenacity measurements were carried out after one washing. For other consecutive washings were done and the tenacity was also measured. The results are shown in Table 5 :

Table 5

	(1)	(2)	(3)	(4)	(5)
after one wash					
Max. load (N)	6.56	6.89	6.93	7.07	7.36
S.D.	0.53	0.41	0.5	0.65	0.42
Tenacity	14.3	15.02	15.11	15.41	16.04
Change in tenacity %	0.0	5.0	5.7	7.8	12.2
after 5 washes					
Max. load (N)	6.77	7.39	8.48	7.6	8.64
S.D.	0.15	0.43	0.42	0.46	0.5
Tenacity	14.776	16.11	18.49	16.57	18.84
Change in tenacity %	0.0	9.1	25.3	12.3	27.6

(1) Control (0 % bis-pantoyl-cystamine, 0% phytantriol)

(2) 0.5 % bis-pantoyl-cystamine

(3) 1.0 % bis-pantoyl-cystamine

(4) 0.5 % bis-pantoyl-cystamine + 0.1 % phytantriol

(5) 1.0 % bis-pantoyl-cystamine + 0.1 % phytantriol

What is claimed is:

1. Hair care compositions comprising bis-pantoyl-cystamine or a derivative thereof.

2. A hair care composition as in claim 1 wherein the bis-pantoyl-cystamine is selected from at least one of RR-, SS-, RS (meso)- and RR/SS- bis-pantoyl-cystamine.

3. A hair care composition as in claim 1 wherein the bis-pantoyl-cystamine is the enantiomeric pair, RR/SS-bis-pantoyl-cystamine, or R,S- (meso-) bis-pantoyl-cystamine, or mixtures thereof.

4. A hair care composition as in claim 1 wherein the bis-pantoyl-cystamine is the diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S- (meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso) : RR/SS is within the range from about 50:50 to about 30:70.

5. A hair care composition as in any one of claims 1-4 wherein bis-pantoyl-cystamine is present in an amount of from about 0.1 wt.-% to about 10 wt.-%.

6. A hair care composition as in any one of claims 1-5 compring additionally one or more agents selected from UV screening agents, vitamin A or derivatives thereof, vitamin C or derivatives thereof, vitamin E or derivatives thereof, a vitamin from the B complex, panthenol, phytantriol or derivatives thereof.

7. A hair care composition as in any one of claims 1-6 compring bis-pantoyl-cystamine, panthenol and/or phytantriol.

8. A hair care composition as claim 7 compring bis-pantoyl-cystamine and phytantriol.

9. A hair care composition as in any one of claims 1 -8 which is a a shampoo, a conditioner, a tonic, a styling gel, a styling mousse, a spray, a pomade, a setting lotion, a colouring or permanent waving composition.

10. The use of bis-pantoyl-cystamine or derivative thereof as a hair strengthening agent in hair care products.

11. The use as in claim 10 wherein the bis-pantoyl-cystamine is selected from at least one of RR-, SS-RS (meso)- and RR/SS- bis-pantoyl-cystamine.

12. The use as in claim 10 wherein the bis-pantoyl-cystamine is the enantiomeric pair, RR/SS-bis-pantoyl-cystamine, or R,S- (meso-) bis-pantoyl-cystamine, or mixtures thereof.

13. The use as in claim 10 wherein the bis-pantoyl-cystamine is the diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S- (meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso) : RR/SS is within the range from about 50:50 to about 30:70.

14. The use as in any one of claims 10-13 wherein bis-pantoyl-cystamine or a derivative thereof is used in an amount of from about 0.1 wt.-% to about 10 wt.-% based on the total weight of the hair care composition.

15. The use as in any one of claims 10-14 wherein bis-pantoyl-cystamine or a derivative thereof is used in combination with one or more agents selected from UV screening agents, vitamin A or derivatives thereof, vitamin C or derivatives thereof, vitamin E or derivatives thereof, a vitamin from the B complex, panthenol, phytantriol or derivatives thereof.

16. The use as in claim 15 wherein bis-pantoyl-cystamine or a derivative thereof is used in combination with panthenol and/or phytantriol.

17. The use as in claim 15 wherein bis-pantoyl-cystamine or a derivative thereof is used in combination with phytantriol.

18. The use as in any one of claims 10-17 wherein the hair care product is a shampoo, a conditioner, a tonic, a styling gel, a styling mousse, a spray, a pomade, a setting lotion, a colouring or permanent waving composition.

19. A method of strenghtening hair which comprises treating hair with a hair care product containing bis-pantoyl-cystamine or a derivative thereof.

20. The method as in claim 18 wherein the bis-pantoyl-cystamine is selected from at least one of RR-, SS-RS (meso)- and RR/SS- bis-pantoyl-cystamine.

21. The method as in claim 19 wherein the bis-pantoyl-cystamine is the enantiomeric pair, RR/SS-bis-pantoyl-cystamine, or R,S- (meso-) bis-pantoyl-cystamine, or mixtures thereof.

22. The method as in claim 18 wherein the bis-pantoyl-cystamine is the diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S- (meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso) : RR/SS is within the range from about 50:50 to about 30:70.

23. The method as in any one of claims 19-22 which comprises treating hair with a hair care product containing bis-pantoyl-cystamine or a derivative thereof in an amount of from about 0.1 wt.-% to about 10 wt.-% based on the total weight of the hair care composition.

24. The method as in any one of claims 19-23 which comprises treating hair with a hair care product containing bis-pantoyl-cystamine or a derivative thereof in combination with one or more agents selected from UV screening agents, vitamin A or derivatives thereof, vitamin C or derivatives thereof, vitamin E or derivatives thereof, a vitamin from the B complex, panthenol, phytantriol or derivatives thereof.

25. The method as in claim 24 which comprises treating hair with a hair care product containing bis-pantoyl-cystamine or a derivative thereof in combination with panthenol and/or phytantriol.

26. The method as in claim 24 which comprises treating hair with a hair care product containing bis-pantoyl-cystamine or a derivative thereof in combination with phytantriol.

27. The method as in any one of claims 19-26 wherein the hair care product is a shampoo, a conditioner, a tonic, a styling gel, a styling mousse, a spray, a pomade, a setting lotion, a colouring or permanent waving composition.

28. RR/SS-bis-pantoyl-cystamine (enantiomeric pair).

29. RS(meso)- bis-pantoyl-cystamine.

30. The diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S- (meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso) : RR/SS is within the range from about 50:50 to about 30:70.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/10682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/06 A61K7/09 A61K7/13 C07C323/23

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 583 257 A (JUNINO ALEX ET AL) 10 December 1996 (1996-12-10) column 1, line 7 - line 57 column 6, line 31 - column 7, line 36 -----	1,6,9, 10,14, 15,18, 19,23, 24,27
A	US 2002/006906 A1 (GEOFFROY HERVE ET AL) 17 January 2002 (2002-01-17) The whole document -----	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2003	17 MAR 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menidjel, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10682

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-27

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27

   Hair care compositions comprising bis-pantoyl-cystamine (3 isomeric forms) or a derivative thereof.

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2. claim: 28

   RR/SS-bis-pantoyl-cystamine (enantiomeric pair).

   ---

3. claim: 29

   RS(meso)-bis-pantoyl-cystamine.

   ---

4. claim: 30

   The diastereomeric mixture of RR/SS-bis-pantoyl-cystamine and R,S-(meso-) bis-pantoyl-cystamine wherein the molar ratio of RS(meso):RR/SS is within the range from 50:50 to 30:70.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/10682

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5583257 A	10-12-1996	FR 2676441 A1	20-11-1992
		US 5449805 A	12-09-1995
		AT 136539 T	15-04-1996
		CA 2068844 A1	18-11-1992
		DE 69209715 D1	15-05-1996
		DE 69209715 T2	31-10-1996
		DK 514282 T3	12-08-1996
		EP 0514282 A1	19-11-1992
		ES 2086094 T3	16-06-1996
		GR 3020118 T3	31-08-1996
		JP 5279322 A	26-10-1993
		US 5334377 A	02-08-1994
US 2002006906 A1	17-01-2002	FR 2807321 A1	12-10-2001
		EP 1147765 A1	24-10-2001
		US 2003185784 A1	02-10-2003