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COSMETIC COMPOSITIONS CONTAINING LACTIC ACID ESTERS OF FATTY ALCOHOLS

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This invention relates to improved cosmetic and pharmaceutical preparations for topical application. The present application is a continuation-in-part of pending application Serial No. 679,120, filed August 20, 1957, now abandoned, entitled "Cosmetic and Pharmaceutical Preparations for Topical Application."

In the application of various cosmetic compositions to the human hair and skin, such as creams, lotions, shampoos, dressings, sticks and the like, it often is the case that there results a detrimental effect on the skin, such as harshness, coarseness, dryness and the like. The present invention is intended and adapted to overcome the disadvantages inherent in prior compositions of the type described, it being among the objects thereof to modify such compositions by the addition thereto of substances capable of overcoming said defects and adapted to improve the condition of the skin.

It is also among the objects of the invention to provide an additive which consists of lactic acid esters which, when combined with the other constituents will enhance their favorable properties.

It is further among the objects of the invention to utilize a process for producing said lactic acid esters which results in properties eminently suitable for the stated purposes.

In practicing the invention, it has been found specifically that fatty alcohol lactic acid esters of straight chain fatty alcohols containing at least eight carbon atoms confer on such preparations a wide range of unusual and most desirable properties and effects on the skin and hair, such as lubricity, emolliency, softening and smoothing, resistance to and protection against the drying effects of alcohol solutions, resistance to water and/or soap or detergents and water, freedom from tactile greasiness or oiliness due to mineral and/or vegetable oils, marked solvency and coupling effects for lanolin, lanolin isolates and derivatives either alone or in the presence of mineral and vegetable oils and freedom from tackiness or greasiness in preparations containing any of the above mentioned materials. Such a range of beneficial properties so markedly enhances the value of, and confers the sought for characteristics in the whole range of cosmetic and pharmaceutical preparations that it is definitely an ingredient of choice in their formulation.

The components of such cosmetic preparations comprise lactic acid esters of straight chain monohydric alcohols derived from naturally occurring fatty acids. These esters may readily be made from lactic acid and alcohols such as capryl, decyl, dodecyl, tetradecyl, hexadecyl, octadecyl and oleyl alcohols. Such alcohols are preferably those which may be obtained by reduction of fatty acids found in coconut type oils and similar oils wherein the fatty acyl radical is reduced to the normal-chain saturated or unsaturated alcohols. The presence of as little as 0.5% of the lactate in cosmetic compositions is sufficient to exert a measurable effect and as much as .35% is in some cases used. In most cases from 1% to 5% is sufficient.

The lactic acid esters may be prepared by utilizing a number of techniques. Thus these compounds may be produced by direct esterification of one molecular weight of lactic acid with an equivalent quantity of the chosen alcohol; again such esters may be prepared by the interchange of the high molecular weight alcohols mentioned for lower molecular weight radicals in lactic acid esters, such as the ethyl radical in ethyl lactate, or again by interesterification of polylactic acid with the described high molecular weight monohydric alcohols.

When the lactic acid esters are made by interesterification between a lower alcohol lactic ester with the higher alcohol, it results in an ester which has poor color and more particularly, very poor and unpleasant odor. It is preferred to produce the esters by direct esterification of the lactic acid with the higher alcohol, thus eliminating the objectional color and odor inherent in esters made by other methods. Pure or technical grade lactic acid is suitable.

The following is a specific example of the preparation of an ester for use in cosmetic and like compositions:

Pure lactic acid, U.S.P. grade, 85% acid (2550 grams) is mixed with dry toluene (3375 ml.) and cetyl alcohol (5453 grams). To this mixture is added concentrated sulfuric acid (18.75 ml. of 96% acid). The mixture is stirred continuously and heated to distill out a constant boiling mixture of toluene and water. At least 802 grams of water are removed, but the accompanying toluene is continuously returned to the mixture. The temperature of the mixture should not be allowed to exceed 130° C.; otherwise excessive darkening of the mixture and considerable odor development occurs.

When the required amount of water has been removed, a solution of soda ash (34.5 grams in about 350 ml. of water) is added to the mixture in order to neutralize the sulfuric acid catalyst. The toluene is then removed from the mixture by distillation under vacuum, and the batch is heated under vacuum until the mixture reaches 110° C. at about 20 mm. of mercury pressure, absolute. The vacuum is then released and the mixture is subsequently steam distilled at atmospheric pressure and 110° C. in order to remove the last traces of toluene.

The mixture is then completely neutralized to an acid number of less than 1.0 by washing the residual oil at 70° C. with a solution of soda ash and salt in water, and finally with hot 10% salt water solution. This washing also removes much of the color and odor found in the crude ester. The color of the batch and the odor may be improved, if desired, by bleaching the material with 2% of its weight of 35% hydrogen peroxide at temperatures ranging from 50° C. at the start to about 110° C. maximum. The bleached material may be dried by heating under vacuum or by mixing with anhydrous sodium sulfate.

It has been found that an ester made this way has properties which are superior to purer material. For example, the ester may be distilled under high vacuum and the distillate is purer than the material we prefer to produce. However, such a pure ester is higher melting and less emollient, and possesses a different feel on the skin, which is less desirable than the refined impure ester that we prefer.

The physical properties of the several lactic acid esters will vary with the characteristics and identity of the particular alcohol employed. Thus cetyl lactate is a crystalline solid at room temperature and melts or liquefies readily on contact with the human skin. Lauryl lactate (dodecyl lactate) is normally liquid at room temperature while stearyl lactate (octadecyl lactate) is normally solid at room temperature and does not melt readily on contact with the human skin. The choice of the particular lactate or mixtures of lactates which are employed in any given formulation will be dictated by the particular use to which the end product is to be put and the characteristics desired to be imparted to such product.

The wide beneficial effect and extensive scope of the

use of the described lactic acid esters can be appreciated and evaluated from a consideration of the characteristics of several typical and illustrative products formulated with these esters as an ingredient or component.

An improved composition for hair dressing or for application to the skin may be produced by dissolving cetyl lactate in ethyl alcohol to the extent of up to about 5 parts per hundred by weight. This solution, packaged as an "aerosol" spray under gas pressure, provides a most excellent hair dressing which markedly softened human hair and imparted a distinct sheen to the hair without leaving a greasy appearance or texture. Such a spray, when applied to the hands, resulted in an excellent and unique hand preparation which imparted an aesthetically smooth, greaseless feeling to roughened and irritated skin. Characteristically, the inclusion of the cetyl lactate completely prevented the dry appearance or feeling which is expectable and usual on application of ethyl alcohol to the skin.

Another hair dressing in accordance with the invention may have the following composition, expressed in parts by weight:

Polyethyleneglycol 600 stearate	9
Lanolin	1
Petrolatum	10
Heavy mineral oil	17
Paraffin wax	5
Isopropyl linoleate	1
Cetyl lactate	2
Preservative	0.1
Triethanolamine	1
Water	54

Similar beneficial effects are achieved by the incorporation of lactic acid esters in rubbing alcohol, such as ethyl or isopropyl alcohol. Thus a preparation comprising about five percent of cetyl, myristyl or lauryl lactate dissolved in about a seventy percent aqueous alcohol solution, when applied to the skin, produced a residual smoothing and lubricating effect which greatly enhanced the beneficial effects derived from the alcohol rub-down. A specific composition of this type is as follows:

Ethyl alcohol	76
Myristyl lactate	4
Water	20

The utilization of the lactic acid esters in hand lotion emulsions also produced unique and desirable results. Thus the addition of from five to about ten percent by weight of cetyl lactate to an emulsified hand lotion imparted very unusual and prolonged lubricity and emolliency to the skin without any appearance of greasiness or tack. The prolongation of these effects are evidently due to the water repellance which the lactate esters impart to residual film on the skin. This lubricating and emollient effect persisted and was marked even after application of water or of soap and water to the skin areas to which the emulsion was applied. This unique water and/or aqueous detergent resistance is characteristic of any skin-protective lotion, cream or other lotion in which such lactic acid esters constitute an ingredient. Such a hand lotion is as follows:

Glycerol monostearate	4
Absorption base, cholesterin	4
Stearic acid	2
Butyl stearate	2
Preservative	0.1
Cetyl lactate	1
Triethanolamine	0.5
Propylene glycol	4
Water	82.4

A most important property of such lactic acid esters, which established them as most desirable ingredients in cosmetic and pharmaceutical preparations is their powerful and unusual solvent and coupling action. This is exemplified in their action with lanolin. For example, up to the order of about twenty parts of anhydrous lanolin are completely and clearly soluble in one hundred parts of lauryl lactate. This resulting solution on application to the skin displayed a remarkable lubricating and emollient action or effect, without any accompanying greasiness or oleaginous or tacky feeling on the skin. It was further ascertained that lauryl acetate, for example, functions as an excellent coupling agent for anhydrous lanolin and mineral oil.

The following composition is illustrative of a hand cream:

Mineral oil	5
Glycerol monostearate	10
Lanolin	2
Butyl stearate	2
Cetyl lactate	2
Preservative	0.1
Propylene glycol	5
Water	74

The efficacy of the described lactic acid esters as solvents and coupling agents for lanolin is a striking and eminently desirable property. For example, in the absence of the lactate esters, anhydrous lanolin presents only partial incomplete solubility in mineral oil. Such solutions do not remain clear for any substantial period of time and the less soluble portions of lanolin precipitate from the solution after some period of storage. However by including small amounts of the lactates in such mixtures, permanent and completely homogeneous solutions of lanolin and mineral oil or of lanolin and vegetable oils are achieved and such solutions do not separate on storage. Here again such solutions on application do not produce any greasy or tacky feeling on the skin or hair.

As indicated, the use of lactic acid esters as beneficially functioning ingredients extends to a wide range of cosmetic products. Such compounds, for example, are especially beneficial adjuvants in lipstick formulations. When solid lactic acid esters, such for example as cetyl or stearyl lactates are incorporated in lipstick bases, marked improvements in the product result. In this particular use, the lactate esters function as solid lubricants and emollients which are much more readily incorporated into the solid wax lipstick bases than are liquids having similar or equivalent emollient or lubricating properties. It is of special note also that the lactates act as very efficient solvents for the halofluorescein dyes used in lipstick bases.

An additional unique, unpredictable and peculiarly beneficial characteristic of certain of this novel group of lactic acid esters is their salutary modifying effect on typical astringent antiperspirant preparations. For example, it has been ascertained that the addition of a small amount of lauryl lactate to an astringent of this type, such as an aluminum chlorohydroxide preparation, completely overcomes and eliminates the unpleasant drag experienced in the application of such astringents in stick, emulsified lotion or cream, spray or solution form.

An antiperspirant lotion may have the following constituents:

Glycerol monostearate	3
Polyoxyethylene laurate-oleate	7
Lanolin	1
Lauryl lactate	2
Propylene glycol	3
Al chlorohydroxide (50% aqueous)	40
Water	44

In a stick form of antiperspirant, the following composition may be considered as typical:

Al chlorohydroxide (50% aqueous)	50
Ethyl alcohol	39
Propylene glycol	3
Cetyl lactate	2
Sodium stearate	6

This new composition, i.e. the astringent preparation containing the lactic acid ester, displays no "roll up" upon application to the skin. Furthermore, the improved composition, when topically applied, is rapidly absorbed and, within less than a minute, there is no evidence or sign that the material has been applied. The benefit conferred by the lactic acid esters on such astringent preparations markedly improves the physical characteristics of such products. The addition of the lactic acid ester produces a material which combines desirably solidity, suitable plasticity and nonfrangible, or crumbling tendencies.

A baby lotion is as follows:

Glycerol monostearate	3
Propylene glycol stearate	3
Sesame oil	10
Cetyl lactate	2
Ethoxylated lanolin	2
Stearic acid	4
Triethanolamine	1
Sorbitol (40% aqueous)	2
Citric acid	1
Water	72

A diaper rash stick may have the following composition:

Cetyl lactate	30
Paraffin wax	17
Olive oil	27
Lanolin	2
Silicone oil	1
Quaternary NH_4 disinfectant	0.25
Ethyl alcohol	10
Stearyl alcohol	10
Ethoxylated lanolin	3

The following composition provides an excellent shampoo cream:

Lanolin	1
Stearic acid	35
Polyethyleneglycol 400 distearate	2
Diethanolamine-fatty acid condensate	3
Magnesium stearate	2
Sodium lauryl sulfate paste	47.2
Preservative	0.1
Lauryl lactate	5
NaOH (50% solution)	0.5
Water	34.5

A typical suntan lotion has the following composition:

Heavy mineral oil	5
Sesame oil	3
Dipropylene glycol methyl ether	1
Glycerol monostearate	6
Lanolin	1
Cetyl lactate	1
Agar gum	1
Water	67.3
Triethanolamine	1
Urea	5
Polyethyleneglycol 400 monolaurate	3
Ethyl-p-gluconylimidobenzoate	2.7
Glycerine	3

A scar treatment cream has the following constituents:

Cetyl lactate	5
Polyethyleneglycol 400 monolinoleate	10
Cetyl alcohol	5
Castor oil	10
Glycerol monostearate	10
Sorbitol (40% aqueous)	2
Water	53
Ethyleneglycol monostearate	5

Other compositions of analogous character embodying the lactic acid esters include brushless shave cream, vanishing cream, night cream, skin cream, foot cream, soap, and many others. Pharmaceutical compositions for topical use are included.

Cosmetic compositions such as described herein may have incorporated therein effective compatible germicidal or preservative materials and especially those which contribute both deodorant and antiseptic properties, such for example as selected non-toxic surface active cationic quaternary amines such as "Hyamine 1622" (di-isobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride) and similar compositions, such as "Hyamine 10–X" and "Hyamine 2389."

The unique water repellency of the residual film of the described lactic acid ester compositions recommends such compositions, having incorporated therein compatible bactericidal and germicidal agents, for the preparation of surgical sites. Such uses are indicative of the wide range of utility of the described lactic acid esters in formulating improved pharmaceutical and cosmetic products. The novel polyfunctional characteristics of the described lactic acid esters establish these compounds as most beneficial ingredients or adjuvants in cosmetic and topical pharmaceutical preparations.

While certain examples of specific cosmetic preparations, comprised of the novel combination of such esters with other ingredients, have been described, it will be understood that these are given as exemplary of the beneficial actions and effects of such esters in the whole range of cosmetic products. Thus the use of these lactic acid esters as desirable ingredients to produce novel combinations possessed of unique properties ramifies through the field of cosmetic products such as lotions, creams, aerosol products, wax base products such as lipsticks, in which the described properties of enhanced lubricity, emolliency, solvency and/or coupling action, water resistance, absence of residual greasiness and tack, are the desiderata.

I claim:

1. A cosmetic composition comprising as essential ingredients a homogeneous dispersion of anhydrous lanolin, a vegetable oil and a straight-chain fatty alcohol lactic acid ester in which the fatty alcohol radical contains eight to eighteen carbon atoms, said composition being film-forming when applied to the human skin,

2. A composition in accordance with claim 1 in which the lactic acid ester is lauryl lactate.

3. An antiperspirant composition comprising as essential ingredients an astringent compound of the complex aluminum halide type with which is incorporated an effective amount of a straight-chain alcohol lactic acid ester in which the fatty alcohol radical contains eight to eighteen carbon atoms, said composition being film-forming when applied to the human skin.

References Cited in the file of this patent

UNITED STATES PATENTS

1,993,736	Graves	Mar. 12, 1935
1,993,737	Graves	Mar. 12, 1935

(Other references on following page)

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16-HYDROXYLATION OF STEROIDS

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This invention relates to, and has for its object the provision of, a method for producing 16-hydroxylated steroids, and more particularly to a microbial process for converting a 16-unsubstituted steroid to its 16-hydroxy derivative.

It has been found that steroids having a methylene group in the 16-position, especially 3-keto or 3-hydroxy steroids, or protected derivatives thereof, either of the androstane (including etiocholane and androstene) series or pregnane (including allopregnane, pregnene and pregnadiene) series, the 3,20-diketo steroids of the pregnane series being particularly preferred, can be converted into useful 16α-hydroxy derivatives by subjecting them to the action of enzymes of *Streptomyces californicus, Streptomyces coelicolor,* or *Streptomyces vinaceus* or to the action of the organisms themselves, under oxidizing and preferably aerobic conditions.

Among the steroids which may be oxygenated by the practice of this invention are those steroids unsubstituted in the 16-position, which are members of: the androstane series, which series includes the androstene and etiocholane series; the estrane series, which series includes the estratriene series; and the pregnane series, which series includes the allopregnane, pregnene and pregnadiene series. Of these, the steroids of the pregnane series, and more particularly the 3,20-diketo steroids of the pregnane series are preferred. Examples of suitable steroids of the pregnane series include progesterone; pregnenolone; pregnanolone; 9β,11β-oxido progesterone; 9β,11β-oxidodesoxy corticosterone; 11β,12β-oxidoprogesterone; 11β,12β-oxidodesoxy corticosterone; hydroxylated progesterones, such as 2α,6α,6β,7,8,9,11α,11β,12α,14,15α, and 15β-hydroxyprogesterone; halogenated progesterone, such as 21-chloroprogesterone; aldosterone; corticosterone; 11-desoxycorticosterone; 17α-hydroxy-11-desoxycorticosterone (Reichstein's compound S); hydrocortisone; prednisolone; 9α-halohydrocortisones (e.g., 9α-fluorohydrocortisone); 9α-halo-prednisolones (e.g., 9α-fluoroprednisolone); 6,9α-dihalohydrocortisones (e.g., 6α,9α-difluorohydrocortisone); and 6,9α-dihaloprednisolones (e.g., 6α,9α-difluoroprednisolone). As indicated before, however, although the preferred starting materials are steroids of the pregnane series, the process of this invention is a general one which may be employed to 16α-hydroxylate other classes of steroids such as those of the androstane series, as exemplified by Δ⁴-androstene-3,17-dione and testosterone; and those of the estrane series, as exemplified by estrone and estradiol.

Among the steroids formed by the process of this invention are the 16α-hydroxy derivatives of the pregnane series, preferably the 16α-hydroxy-3,20-diketo-steroids of the pregnane series. Examples of resulting products of the 16α-hydroxy pregnane series include 16α-hydroxyprogesterone; the 16α-hydroxy derivatives of hydroxylated progesterone; the 16α-hydroxy derivatives of halogenated progesterone; 16α-hydroxyaldosterone; 16α-hydroxycorticosterone; 16α-hydroxy-11-desoxycorticosterone; 16α,17α-dihydroxy-11-desoxycorticosterone; 16α-hydroxyhydrocortisone; 16α-hydroxyprednisolone; 9α-halo-16α-hydroxyhydrocortisones (e.g., 9α-fluoro-16α-hydroxyhydrocortisone); 9α-halo-16α-hydroxyprednisolones (e.g., triamcinolone); 6,9α-dihalo-16α-hydroxyhydrocortisones (e.g., 6α,9α-difluoro-16α-hydroxyhydrocortisone); and 6,9α-dihalo-16α-hydroxyprednisolones (e.g., 6α,9α-difluoro-16α-hydroxyprednisolone). If a steroid of the androstane series is hydroxylated, the 16α-hydroxy derivative is also formed as exemplified by 16α-hydroxy-Δ⁴-androstene-3,17-dione and 16α-hydroxytestosterone. If a steroid of the estrane series is hydroxylated, the 16α-hydroxy derivative is also formed as exemplified by 16α-hydroxyestrone and 16α-hydroxy estriol.

The action of the enzymes of *Streptomyces californicus, Streptomyces coelicolor,* or *Streptomyces vinaceus* to produce 16α-hydroxy steroids can be utilized either by including the steroid in an aerobic culture of the microorganism, or by bringing together, in an aqueous medium, the steroid, air, and enzymes of non-proliferating cells of the microorganism.

In general, the conditions of culturing the Streptomyces for the purposes of this invention are (except for the inclusion of the steroid to be converted) the same as those of culturing various Streptomyces for the production of antibiotics and/or vitamin B_{12}, i.e., the microorganism is aerobically grown in contact with (in or on) a suitable fermentation medium. A suitable medium essentially comprises a source of nitrogenous and growth-promoting factors, and an assimilable source of carbon and energy. The latter may be a carbohydrate and/or the steroid itself. Preferably, however, the medium includes an assimilable source of carbon and energy in addition to the steroid.

The nitrogen source materials may be organic (e.g. soybean meal, cornsteep liquor, meat extract and/or distillers solubles) or synthetic (i.e., composed of simple, synthesizable organic or inorganic compounds such as ammonium salts, alkali nitrates, amino acids, urea or thiourea).

As to the source material, lipids, especially (1) fatty acids having at least 14 carbon atoms, (2) fats or (3) mixtures thereof, may be used. Examples of such fats are lard oil, soybean oil, linseed oil, cottonseed oil, peanut oil, fancy mutton tallow, sperm oil, olive oil, tristearin, tripalmitin, triolein and trilaurein, and illustrative fatty acids include stearic, palmitic, oleic, linoleic and myristic acids.

Other carbon-containing materials may also be used. For example, such materials as glycerol, glucose, fructose, sucrose, lactose, maltose, dextrins, starches, whey, etc., are adequate carbon source materials. These materials may be used either in purified state or as concentrates, such as whey concentrate, corn, wheat or barley mash; or mixtures of the above may be employed. It is to be noted, however, that the steroid is added to the fermentation medium essentially as a precursor and not as an energy source.

The following examples are illustrative of the invention:

EXAMPLE 1

(a) *Fermentation*

Surface growth from each of five two-week old agar slant cultures of *Streptomyces californicus,* WC 3312 (Culture Collection, Institute of Microbiology, Rutgers University, New Brunswick, New Jersey), the slant containing as a nutrient medium (A):

	Grams
Glucose	10
Yeast extract	2.5
K_2HPO_4	1
Agar	20

Distilled water to 1 liter.

is suspended in 2.5 ml. of a 0.01% sodium lauryl sulphate aqueous solution. One ml. portions of the suspension are used to inoculate ten 250 ml. conical flasks, each