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PATENT SPECIFICATION

NO DRAWINGS

965.301

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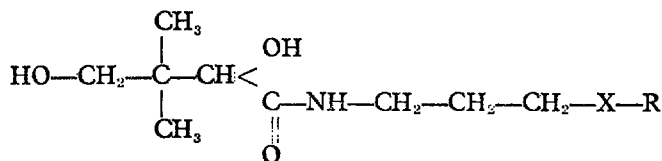
COMPLETE SPECIFICATION

Novel Ethers and a process for their manufacture

We, F. HOFFMANN-LA ROCHE & CO. AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel ethers and salts thereof and a process for their manufacture. 10

The novel ethers provided by the invention are compounds of the general formula:



wherein the symbol X is an oxygen or sulphur atom and the symbol R is an alkyl, alkenyl or dialkylamino-alkyl group or a heterocyclic-substituted acyclic hydrocarbon radical or an alkyl-substituted cycloaliphatic hydrocarbon radical or an alkoxy-substituted aromatic hydrocarbon radical, and acid addition and quaternary salts of those compounds which contain a tertiary nitrogen atom in the [thio]-ether portion. They are useful as cosmetic agents and as medicaments in that they exhibit pantothenic acid activity on peroral or percutaneous administration. In contrast to the known acyl-panthenols they are very stable and therefore are particularly suitable for both applications. 15
acyclic
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The novel substances aforesaid possess an excellent water-solubility; the lower members being miscible with water in all proportions while the higher members are still very soluble. They are readily soluble in the common organic solvents (e.g. ethyl alcohol, diethyl ether, ethyl acetate and acetone) and the solutions obtained are especially suitable for percutaneous application (e.g. cosmetic preparations). They may be made up into cosmetic preparations (e.g. hair-washes, hair oils, salves [Price 4s. 6d.] 35
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and preparations for the care of the skin) in the usual manner using aqueous alcohols, paraffin oil and fatty substances for example. Perfuming agents and other useful additives may also be incorporated. 45

The novel substances aforesaid may also be used in pharmaceutical preparations which contain them in admixture with a pharmaceutical organic or inorganic inert carrier material suitable for enteral or parenteral administration (e.g. water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols or petroleum jelly). The preparations may be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). If required they may be sterilised and/or contain additive materials, for example, conserving, stabilising, wetting or emulsifying agents, salts for variation of the osmotic pressure or buffers. They may also contain yet other therapeutically valuable materials. 50
55
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additive.

The alkyl group denoted by R in the foregoing formula may, for example, be the methyl, ethyl or n-decyl group. Examples of alkenyl groups are allyl, phetyl and geranyl. The 65



dialkylamino-alkyl group denoted by R can be the dimethylamino-ethyl or diethylamino-ethyl radical. Examples of heterocyclic-substituted acyclic radicals are the piperidino-ethyl and tetrahydro-furfuryl radicals. A suitable alkyl-substituted *cycloalkyl* value of R is menthyl. A useful alkoxy-substituted aromatic value of R is guaiacyl. The preferred compound is that in which X is an oxygen atom and R is the ethyl radical.

According to the process provided by the invention, the foregoing novel substances are manufactured by reacting racemic or optically active α - hydroxy - β, β - dimethyl - *gamma*-butyrolactone with an amine of the general formula



wherein the symbols X and R have the significance given earlier, and converting if desired the [thio]ether product (if containing a tertiary nitrogen atom in the [thio]ether portion) into an acid addition or quaternary salt.

The amines of the general formula second written can conveniently be prepared by the addition of the appropriate alcohols or thiols to acrylonitrile and hydrogenating the cyano group in the addition product.

The reaction is advantageously carried out without the use of a solvent. On mixing both reaction components, reaction immediately sets in. It is advantageous to use equimolar amounts of the reaction components. After the initial evolution of heat has died down it is advisable to maintain the reaction mixture at a temperature of 40°—80°C for a few hours. The preferred amine starting material is one in which the symbol X is an oxygen atom and the symbol R is the ethyl radical. The basic [thio]ethers of the invention can be converted into their acid addition salts by treatment with acids (for example, hydrohalic acids such as hydrochloric acid and hydrobromic acid, nitric acid, sulphuric acid and phosphoric acid) or into their quaternary salts by treatment with quaternising agents (for example, alkyl halides such as methyl bromide and ethyl iodide and dialkyl sulphates such as dimethyl sulphate).

The novel [thio]ethers of the invention, which are obtainable in quantitative yield by the foregoing process, are either colourless liquids which are readily soluble in water and in the common organic solvents (e.g. alcohols, ketones and ether) or low-melting crystalline solids. They may be purified by distillation in a high vacuum but it should be borne in mind that the optically active compounds may be partially or wholly racemised by such procedure.

In order that the process of the invention may be more clearly understood and readily carried into effect, the following Examples are given by way of illustration:

EXAMPLE 1

To 130 g of D(-)- α -hydroxy- β, β -dimethyl-*gamma*butyrolactone are added in one portion at ca 20°C while stirring 89 g of 3-methoxy-propyl amine. The reaction occurs immediately with self-heating. The temperature rises to about 50°C and after the reaction has died down the mixture is maintained for a further 2 hours at the same level. The D(+)- α, γ -dihydroxy - N - (3 - methoxy - propyl) - β, β -dimethyl-butylamide [methyl ether] which is obtained in quantitative yield is a colourless liquid which is readily soluble in water and the common organic solvents (e.g. alcohols, ketones, diethyl ether); $[\alpha]_{\text{D}}^{20} = +28.0^\circ$ ($c = 3.0075$ in water). By distillation in a high vacuum partial racemisation sets in.

The 3-methoxy-propyl amine is prepared by catalytical hydrogenation of 3-methoxy-propionitrile in methanol in the presence of ammonia; boiling point = 114°—116°C/760 mm.Hg.

In an analogous manner there are prepared from 3-ethoxy-propyl amine (boiling point 130°—132°C/760 mm Hg) the ethyl ether, $[\alpha]_{\text{D}}^{20} = +27.8^\circ$ ($c = 2.8935$ in water); from 3-*n*-decyloxy-propyl amine (boiling point 145°—147°C/11 mm Hg) the *n*-decyl ether, $[\alpha]_{\text{D}}^{20} = +28.75^\circ$ ($c = 3.1125$ in methanol); from 3 - (tetrahydro - furfuryloxy) - propyl amine (boiling point 100°—102°C/10 mm Hg) the tetrahydro-furfuryl ether, $[\alpha]_{\text{D}}^{20} = +20.01^\circ$ ($c = 3.135$ in water); and from 3-(*o*-methoxy-phenoxy)-propyl amine (boiling point 144°—147°C/10 mm Hg melting point of the hydrochloride 123°—124°C) the guaiacol ether, $[\alpha]_{\text{D}}^{20} = +26.29^\circ$ ($c = 3.05$ in methanol).

EXAMPLE 2

115 g of 3-allyloxy-propyl amine are mixed with 130 g of D(-)- α -hydroxy- β, β -dimethyl-*gamma*butyrolactone while stirring. The temperature rises from 26° to 45°C with the immediate setting in of the reaction. After the reaction has died down, the mixture is maintained for two hours at 50°C. The D(+)- α, γ -dihydroxy - N - (3 - allyloxy - propyl) - β, β -dimethyl-butylamide [allyl ether] is miscible with water and ether in all proportions; $[\alpha]_{\text{D}}^{20} = +18.32^\circ$ ($c = 3.0075$ in water).

The 3-allyloxy-propyl amine results by the reduction of 3-allyloxy-propionitrile with lithium aluminium hydride; boiling point 47°—49°C/11 mm Hg.

In an analogous manner there is prepared from 3 - geranyloxy - propyl amine (boiling point 138°—140°C/10 mm Hg) the geranyl ether, $[\alpha]_{\text{D}}^{20} = +27.5^\circ$ ($c = 3.086$ in methanol); and from 3-phytyloxy-propyl amine (boiling point 168°—170°C/0.04 mm Hg) the phytyl ether, $[\alpha]_{\text{D}}^{20} = +13.37^\circ$ ($c = 3.035$ in methanol).

EXAMPLE 3

130 g of D(-)- α -hydroxy- β, β -dimethyl-*gamma*butyrolactone are added in one portion



to 119 g of 3-ethylthio-propyl amine while stirring. The reaction occurs immediately and the temperature rises from 25° to 50°C. After the reaction has died down, the mixture is maintained for a further 3 hours at 50°C. The D(+)- α,γ -dihydroxy-N-(3-ethylthio-propyl)- β,β -dimethyl-butyramide [ethyl thioether] is readily soluble in water and the common organic solvents; $[\alpha]_D^{20} = +21.85^\circ$ (c=3.478 in water).

The 3-ethylthio-propyl amine results by the reduction of 3-ethylthio-propionitrile with lithium aluminium hydride; boiling point 70°—72°C/11 mm Hg.

EXAMPLE 4

130 g of D(-)- α -hydroxy- β,β -dimethyl-*gammabutyrolactone* is mixed up by stirring with 174 g of 3-(diethylamino-ethoxy)-propyl amine. As the reaction sets in immediately, the temperature rises from 25° to 50°C and, after the reaction has died down the mixture is maintained for a further 2 hours at this level. The diethylamino-ethyl ether is colourless, readily soluble in water with a strong alkaline reaction and readily soluble in organic solvents. With acids it forms soluble neutral salts; $[\alpha]_D^{20} = +20.64^\circ$ (c=3.112 in water) for the base; $[\alpha]_D^{20} = +17.85^\circ$ (c=10 in water) for the hydrochloride.

EXAMPLE 5

To 130 g of D(-)- α -hydroxy- β,β -dimethyl-*gammabutyrolactone* are added in one portion while stirring 213.3 g of L(-)-3-menthyloxy-propyl amine. The temperature rises immediately to 48°C and the mixture is then maintained at 75°C for 2 hours by warming. The viscous reaction product is dissolved in 500 ml of low boiling petroleum ether and allowed to stand in ice for completion of the crystallization. The product is filtered off under suction and dried in a vacuum. The D(-)- α,γ -dihydroxy-N-(3-menthyloxy-propyl)- β,β -dimethyl-butyramide [L(-)-menthyl ether] formed melts at 52°—54°C; $[\alpha]_D^{20} = -28.21^\circ$ (c=3 in methanol).

The L(-)-3-menthyloxy-propyl amine is prepared by catalytic hydrogenation of L(-)-3-menthyloxy-propionitrile (boiling point 161°—163°C/18 mm Hg) in the presence of ammonia (boiling point 145°—147°C/16 mm Hg; $[\alpha]_D^{20} = -88.04^\circ$ (c=3.1 in methanol)).

EXAMPLE 6

130 g of D(-)- α -hydroxy- β,β -dimethyl-*gammabutyrolactone* are added to 146 g of 3-(dimethylamino-ethoxy)-propyl amine—whereupon immediate liquefaction and warming occurs. The mixture is maintained for a further 2 hours at 50°C. The colourless, slightly liquid dimethylamino-ethyl ether is obtained in quantitative yield.

To a solution of 276 g of this ether in 1000 ml of acetone are added 95 g of methyl

bromide dissolved in 500 ml of acetone. The temperature rises to 48°C whereupon the oily bromocholine ether formed separates out. The precipitation is completed by the addition of diethyl ether. The bromocholine ether is colourless and readily soluble in water; $[\alpha]_D^{20} = +16.25^\circ$ (c=3.25 in water).

The 3-(dimethylamino-ethoxy)-propyl amine is prepared by catalytic hydrogenation of 3-(dimethylamino-ethoxy)-propionitrile (boiling point 118°C/17 mm Hg) in the presence of ammonia (boiling point 93°—94°C/19 mm Hg).

The following are Examples of the way in which the novel substances of the invention may be made up into cosmetic and/or pharmaceutical preparations:

EXAMPLE A.

1—5 parts by weight of the ethyl ether (see Example 1) are dissolved in 100 g of 50% (wt/vol) aqueous ethyl or isopropyl alcohol with slight warming. The mixture is coloured and perfumed according to desire.

After cooling, it is made up to 1000 parts by volume with the corresponding 50% (wt/vol) alcohol/water mixture and there is obtained an active preparation for the treatment of the scalp and the hair.

EXAMPLE B

1—5 g of the phytol ether (see Example 2) are dissolved in 100 g of paraffin oil with slight warming. It can be coloured and perfumed according to desire. Subsequently, the solution is made up to 1000 g with paraffin oil. There is obtained an active hair oil which is especially suitable for the treatment of dry scalp, dry dandruff and brittle hair.

EXAMPLE C

5.00 g of glycerine monostearate, 1.00 g of cetyl alcohol, 1.00 g of lanolin, 10.00 g of isopropyl-myristal, 10.00 g of aceto stearate, 5.00 g of bees wax and 20.00 g of (ethoxylated fatty alcohol)/(phosphoric acid ester) are warmed to 60°C. Subsequently, a solution of 5.00 g of the ethyl ether (see Example 1) is introduced into the melt. While stirring, 918 g of water are slowly worked in at 50°C. The emulsion can be perfumed and coloured according to desire. There is thus obtained an agent for the treatment of the hands which is particularly suitable for the treatment of rough, dry and cracked skin.

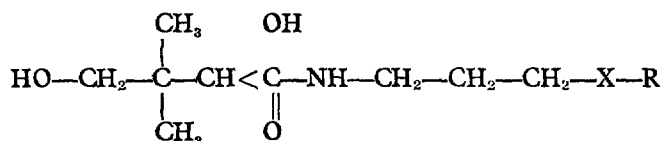
EXAMPLE D

30.00 g of glycerine monostearate, 20.00 g of stearyl alcohol, 20.00 g of cetyl alcohol, 20.00 g of isopropyl-myristal, 10.00 g of lanolin, and 30.00 g of (ethoxylated fatty alcohol)/(phosphoric acid ester) are melted at 60°C. A solution of 5.00 g of the ethyl ether (see Example 1) and 5.00 g of the ethyl thioether (see Example 3) in 860 g of water is

slowly stirred into this melt at 50°C. This emulsion, which is especially suitable for the treatment of dry and impure facial skin, can be coloured and perfumed according to desire.

EXAMPLE E

There is manufactured a salve which contains 4 parts per cent (wt/vol) of cetyl alcohol, 10 parts per cent (wt/vol) of lanolin and 86 parts per cent (wt/vol) of white petroleum jelly. 75 g of this salve is allowed to mellow at 40°C — whereupon a mixture of 5 g of panthenol ethyl ether and 20 g of water is emulsified in under mechanical machining.



wherein the symbol X is an oxygen or sulphur atom and the symbol R is an alkyl, alkenyl or dialkylamino-alkyl group or a heterocyclic-substituted acyclic hydrocarbon radical or an alkyl-substituted cycloaliphatic hydrocarbon radical or an alkoxy-substituted aromatic hydrocarbon radical, and acid addition and quaternary salts of those compounds which contain a tertiary nitrogen atom in the [thio]-ether portion.

2) An ether as claimed in claim 1 hereof, wherein X is an oxygen atom and R is the ethyl radical.

3) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises reacting racemic or optically active α - hydroxy - β, β - dimethyl - γ - butyrolactone with an amine of the general formula:



wherein the symbols X and R have the significance given in claim 1, and converting if

EXAMPLE F

5 g of panthenol ethyl ether are admixed with 45 g of water. 10 g of polyoxyethylene sorbitol monostearate (Mixture A) are dissolved in this mixture while stirring at 70°C. 30 g of hydrogenated peanut oil and 10 g of glycerine are melted together and likewise warmed to 70°C (Mixture B). Mixtures A and B are then mixed at 70°C and emulsified. Then, it is cooled down with constant stirring until it has attained a salve-like consistency.

WHAT WE CLAIM IS:—

1) Ethers of the general formula:

desired the [thio]ether product (if containing a tertiary nitrogen atom in the [thio]ether portion) into an acid addition or quaternary salt.

4) A process in accordance with claim 3, wherein the amine starting material used is one in which the symbol X is an oxygen atom and the symbol R is the ethyl radical.

5) A process for the manufacture of the substances claimed in claim 1 hereof, substantially as described with reference to the Examples.

6) Ethers as claimed in claim 1 hereof and salts thereof, when manufactured by the process claimed in any one of claims 3—5 inclusive.

7) A cosmetic or pharmaceutical preparation comprising one or more of the ethers claimed in claim 1 hereof, or salts thereof, in association with a compatible carrier.

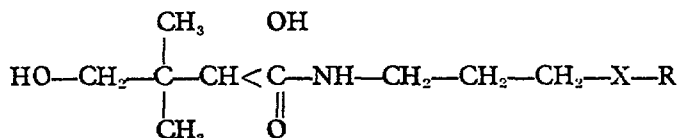
W. D. WHITAKER,
Patent Agent,

For F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

slowly stirred into this melt at 50°C. This emulsion, which is especially suitable for the treatment of dry and impure facial skin, can be coloured and perfumed according to desire.

EXAMPLE E

There is manufactured a salve which contains 4 parts per cent (wt/vol) of cetyl alcohol, 10 parts per cent (wt/vol) of lanolin and 86 parts per cent (wt/vol) of white petroleum jelly. 75 g of this salve is allowed to mellow at 40°C — whereupon a mixture of 5 g of panthenol ethyl ether and 20 g of water is emulsified in under mechanical machining.



wherein the symbol X is an oxygen or sulphur atom and the symbol R is an alkyl, alkenyl or dialkylamino-alkyl group or a heterocyclic-substituted acyclic hydrocarbon radical or an alkyl-substituted cycloaliphatic hydrocarbon radical or an alkoxy-substituted aromatic hydrocarbon radical, and acid addition and quaternary salts of those compounds which contain a tertiary nitrogen atom in the [thio]-ether portion.

2) An ether as claimed in claim 1 hereof, wherein X is an oxygen atom and R is the ethyl radical.

3) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises reacting racemic or optically active α -hydroxy- β,β -dimethyl- γ -butyrolactone with an amine of the general formula:



wherein the symbols X and R have the significance given in claim 1, and converting if

EXAMPLE F

5 g of panthenol ethyl ether are admixed with 45 g of water. 10 g of polyoxyethylene sorbitol monostearate (Mixture A) are dissolved in this mixture while stirring at 70°C. 30 g of hydrogenated peanut oil and 10 g of glycerine are melted together and likewise warmed to 70°C (Mixture B). Mixtures A and B are then mixed at 70°C and emulsified. Then, it is cooled down with constant stirring until it has attained a salve-like consistency.

WHAT WE CLAIM IS:—

1) Ethers of the general formula:

desired the [thio]ether product (if containing a tertiary nitrogen atom in the [thio]ether portion) into an acid addition or quaternary salt.

4) A process in accordance with claim 3, wherein the amine starting material used is one in which the symbol X is an oxygen atom and the symbol R is the ethyl radical.

5) A process for the manufacture of the substances claimed in claim 1 hereof, substantially as described with reference to the Examples.

6) Ethers as claimed in claim 1 hereof and salts thereof, when manufactured by the process claimed in any one of claims 3—5 inclusive.

7) A cosmetic or pharmaceutical preparation comprising one or more of the ethers claimed in claim 1 hereof, or salts thereof, in association with a compatible carrier.

W. D. WHITAKER,
Patent Agent,

For F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

