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PATENT SPECIFICATION

NO DRAWINGS

1061457



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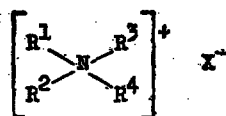
COMPLETE SPECIFICATION

Novel Quaternary Ammonium Compounds and a Process for the Manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESSELLSCHAFT a Swiss Company of 124—184 Grenzachstrasse, 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 is concerned with novel quaternary ammonium compounds and a process for the manufacture thereof.

The novel quaternary ammonium compounds provided by the invention may be formulated thus:



(I)

wherein two of the substituents R^1 , R^2 , R^3 and R^4 represent decyl groups, another of the substituents represents a lower-alkenyl, lower-alkynyl, lower hydroxy-alkyl, lower alkoxy-alkyl, lower carboxyl-alkyl or lower carbalkoxy-alkyl group, the other substituent represents a lower-alkyl, lower-alkenyl or lower-alkynyl group and X represents the anionic moiety of an acid.

The novel quaternary ammonium compounds provided by this invention are useful as fungicides or fungistatic agents. In particular, they are active against the dermatophytes which predominantly cause foot mycosis (e.g. *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Epidermophyton floccosum*) as well as against other dermatophytes (e.g. *Trichophyton schoenleinii* and *Microsporum canis*). They are also active against yeasts such as *Candida albicans*, mould fungi such as *Aspergillus fumigatus* and bacteria such as *Streptococci*, *Staphylococci*, *Coli* and *Pyocyanus*. They accordingly exhibit a broad antimicrobial spectrum. Since foot mycosis can be copendent on yeasts and bacteria, the aforesaid compounds are especially suitable for this indication.

The novel quaternary ammonium compounds provided by the invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. This carrier may be an organic or inorganic inert carrier material suitable for local application such as, for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols or petroleum jelly. The pharmaceutical preparations can, for example, be submitted in powder form or in liquid form; for example as a solution, a suspension, an emulsion or an aerosol. They may contain additives such as preserving, stabilizing, wetting or emulsifying agents or buffers. They can also contain other therapeutically valuable materials. The pharmaceutical preparations suitably contain from about 0.2 to 5% of the novel compounds provided by the invention.

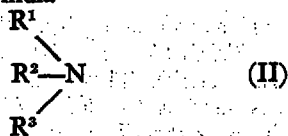
It will be appreciated that the terms "lower alkyl", "lower alkenyl", "lower alkynyl", "lower hydroxy - alkyl", "lower alkoxy-alkyl", "lower carboxy - alkyl" and "lower carbalkoxy - alkyl" are used in this description and in the accompanying claims to mean

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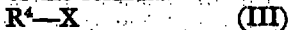
carboxy

straight-chain or branched-chain alkyl, alkenyl, alkynyl, hydroxy-alkyl, alkoxy-alkyl, carboxy-alkyl and carbalkoxy-alkyl groups containing not more than seven carbon atoms. Examples of these groups are, for example, methyl and ethyl, allyl, dimethyl-allyl and α -methyl-allyl, propargyl and α -methyl-propargyl, hydroxy-methyl, hydroxy-ethyl and hydroxy-butyl, methoxy-methyl, methoxy-ethyl and ethoxy-methyl, carboxy-methyl and carboxy-ethyl and carbomethoxy-methyl, carbethoxy-methyl and carbomethoxy-ethyl. The anionic moiety can be either organic or inorganic. It can, for example, be a halide anion such as chloride, bromide or iodide or the anion of a sulphur-containing organic acid, especially a sulphonic acid such as methane-sulphonic acid, benzene-sulphonic acid or toluene-sulphonic acid. The chloride and bromide anions and the anion of methane-sulphonic acid are preferred.

According to the process provided by the invention, the novel compounds of formula I are manufactured by quaternizing a tertiary amine of the formula



with a compound of the formula



in which formulae R^1 , R^2 , R^3 , R^4 and X have the significance given earlier.

The tertiary amine starting materials of formula II are essentially known substances and can be prepared by the usual methods from primary or secondary amines by introduction of the desired substituent.

The quaternization is suitably effected using the tertiary amine of formula II and the compound of formula III in about equimolar amounts. This quaternization is conveniently effected in the presence of an inert solvent such as acetone, alcohol, ethyl acetate, N,N -dimethyl-formamide or petroleum ether. The temperature is not critical, but it is preferred to operate at an elevated temperature (preferably between about 50°C and 130°C).

In a preferred embodiment of the process, a tertiary amine of formula II is quaternised with a compound of formula III in which R^4 is a lower-alkenyl, lower-alkynyl, lower hydroxy-alkyl, lower alkoxy-alkyl, lower carboxy-alkyl or a lower carbalkoxy-alkyl group.

The following examples illustrate the process provided by the invention.

EXAMPLE 1.

100 g of didecyl methyl amine were dissolved in 300 ml of acetone and treated with 50 g of allyl bromide. The mixture was boiled under reflux for 5 hours. The solvent was distilled off, the viscous residue extracted three times with 500 ml of petroleum ether (boiling range 40°C — 45°C) each time and

dried in vacuum at 50°C . Didecyl allyl methyl ammonium bromide was obtained as a colourless hygroscopic wax of melting point 40°C — 45°C .

EXAMPLE 2.

100 g of didecyl methyl amine were dissolved in 300 ml of acetone and treated with 30 g of allyl chloride. The mixture was boiled under reflux for 5 hours. After distilling off the solvent, the residue was dissolved in 500 ml of 80% aqueous methanol and this methanol solution was extracted three times with 200 ml of petroleum ether (boiling range 40°C — 45°C) each time. The methanol solution was then evaporated *in vacuo* and the residue dried *in vacuo*. Didecyl allyl methyl ammonium chloride was obtained as a colourless, viscous and hygroscopic oil which in time solidified.

EXAMPLE 3.

100 g of didecyl allyl amine were dissolved in 400 ml of petroleum ether (boiling range 40°C — 45°C) and 37.5 g of dimethyl sulphate were added dropwise with stirring. The mixture was heated under reflux for two hours and allowed to stand overnight. On the next day, the paste obtained was filtered off and rewashed with petroleum ether. The salt was dried *in vacuo* over phosphorus pentoxide. Didecyl allyl methyl ammonium methosulphate was obtained as a white wax of melting point 30°C — 33°C .

EXAMPLE 4.

100 g of didecyl methyl amine were dissolved in 500 ml of petroleum ether (boiling range 40°C — 45°C), treated with 60 g of dimethyl-allyl bromide and heated under reflux for 4 hours. After cooling, the precipitated salt was filtered off, washed with petroleum ether and dried *in vacuo*. Didecyl dimethyl-allyl methyl ammonium bromide was obtained as a white, hygroscopic powder of melting point 66°C — 67°C .

EXAMPLE 5.

100 g of didecyl methyl amine were dissolved in 400 ml of petroleum ether (boiling range 40°C — 45°C), treated with 40 g of propargyl bromide and heated under reflux for 5 hours. After cooling, the oil which precipitated was separated, washed several times with petroleum ether and dried *in vacuo*. Didecyl propargyl methyl ammonium bromide was obtained as a reddish, viscous oil;

$$n_D^{25} = 1.4967.$$

EXAMPLE 6.

100 g of didecyl allyl amine were dissolved in 400 ml of absolute ether and treated with 40 g of allyl bromide. The mixture was heated under reflux for 5 hours. After evaporation of the ether, the oily residue was extracted three times with 300 ml of petroleum ether (boiling range 40°C — 45°C) each time and the insoluble oil was dried *in vacuo*. Didecyl

diallyl ammonium bromide was obtained as a colourless, viscous oil; $n_D^{24} = 1.4985$.

EXAMPLE 7.

100 g of didecyl propargyl amine were dissolved in 300 ml of petroleum ether (boiling range 40°—45°C), treated with 40 g of propargyl bromide and heated under reflux for 5 hours. After cooling, the liquid was decanted from the precipitated oil and the oil was extracted twice with 300 ml of petroleum ether (boiling range 40°—45°C) each time. The insoluble oil was dried *in vacuo*. Didecyl dipropargyl ammonium bromide was obtained as a colourless, viscous oil; $n_D^{26} = 1.5023$.

EXAMPLE 8.

100 g of didecyl propargyl amine were dissolved in 400 ml of acetone, treated with 40 g of allyl bromide and heated under reflux for 2 hours. The solvent was distilled off and the residue extracted three times with 300 ml of petroleum ether (boiling range 40°—45°C) each time. The insoluble oil was dried *in vacuo*. Didecyl allyl propargyl ammonium bromide was obtained as a colourless, viscous oil; $n_D^{22} = 1.5032$.

EXAMPLE 9.

100 g of didecyl methyl amine were dissolved in 400 ml of acetone, treated with 40 g of ethylene-bromohydrin and heated under reflux for 5 hours. After evaporation of the acetone, the oil which remained was extracted three times with 200 ml of petroleum ether (boiling range 40°—45°C) each time and the insoluble oil was dried *in vacuo*. Didecyl hydroxy-ethyl methyl ammonium bromide was obtained as a slightly red-coloured, viscous oil; $n_D^{28} = 1.4860$.

EXAMPLE 10.

100 g of didecyl methyl amine were dissolved in 400 ml of acetone, treated with 50 g of bromoethyl methyl ether and the solution was heated under reflux for 5 hours. The solvent was distilled off and the residue extracted three times with 200 ml of petroleum ether (boiling range 40°—45°C) each time. The insoluble oil was dried *in vacuo*. Didecyl methoxy-ethyl methyl ammonium bromide was obtained as a yellow, hygroscopic wax of melting point 64°—66°C.

EXAMPLE 11.

100 g of didecyl methyl amine were dissolved in 400 ml of ethanol, treated with 60 g of methoxy-butyl bromide and the solution heated under reflux for 4 hours. After evaporation of the solvent, the residue was

extracted three times with 200 ml of petroleum ether (boiling range 40°—45°C) each time and the insoluble oil dried *in vacuo*. Didecyl methoxy-butyl methyl ammonium bromide was obtained as a yellow, viscous oil; $n_D^{28} = 1.4873$.

EXAMPLE 12.

100 g of didecyl methyl amine were dissolved in 400 ml of acetone, treated with 45 g of chloro-acetic acid ethyl ester and this solution was heated under reflux for 5 hours. After evaporation of the solvent, the residue was extracted three times with 200 ml of petroleum ether (boiling range 40°—45°C) each time and the insoluble oil dried *in vacuo*. Didecyl carboethoxy-methyl methyl ammonium bromide was obtained as a colourless wax of melting point 42°—45°C.

The following Examples illustrate pharmaceutical preparations containing the novel quaternary ammonium compounds provided by the invention and the manner in which the preparations can be obtained.

EXAMPLE A.

A paste containing 2.0 g of didecyl allyl methyl ammonium bromide, 3.0 g of titanium dioxide, 2.00 g of deodorized lanolin, 3.0 g of yellow petroleum jelly, 6.0 g of stearin, 6.0 g of cetyl alcohol, 5.0 g of polyoxy-ethylene-sorbitan monostearate and distilled water to 100.0 g was prepared as follows:

The deodorized lanolin, yellow petroleum jelly, stearin, cetyl alcohol and polyoxy-ethylene-sorbitan monostearate in the foregoing amounts were melted with each other on a steam-bath to give a hot melt. The hot water (about 75°C) was added to this hot melt (about 70°—75°C) in a spray. The whole was cold-stirred at room temperature. In doing this, the evaporated water was continuously replaced with distilled water. This yielded an ointment base.

After individually finely sieving, the active material and titanium dioxide were mixed with each other. The ointment base was gradually admixed with the powder mixture of active material and titanium dioxide, attention being paid that the powder mixture was well ground with the ointment base and finely divided in the latter. Evaporated water was replaced.

EXAMPLE B.

A salve containing 1 g of didecyl allyl methyl ammonium bromide, 4 g of silicic acid, 20 g of titanium dioxide, 20 g of talc, 15 g of pure glycerine and distilled water to 100 g was prepared as follows:

The active material was dissolved in the water at about 50°C. The silicic acid was worked up in a mortar at room temperature by means of a homogenizer to give a homogeneous mixture and then mixed with the



80

2.0 g

85

monostearate

90

95

100

105

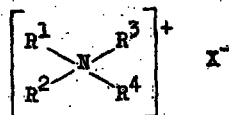
110

115

glycerine. The aqueous solution of the active material was then added to the mixture of silicic acid and glycerine and homogenized with the aid of a homogenizer. A finely sieved mixture of the titanium dioxide and talc was added portionwise to this mixture. Homogenization was effected after each added portion by means of a homogenizer so that a fine, lump-free salve was formed. After replacement of evaporated water, the finished salve was filled into tubes which were immediately closed.

WHAT WE CLAIM IS:—

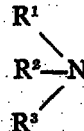
- 1) A quaternary ammonium compound of the formula



wherein two of the substituents R^1 , R^2 , R^3 and R^4 represent decyl groups, another of the substituents represents a lower-alkenyl, lower-alkynyl, lower hydroxy-alkyl, lower alkoxy-alkyl, lower carboxy-alkyl or lower carbalkoxy-alkyl, the other substituent represents a lower-alkyl, lower-alkenyl or lower-alkynyl group and X represents the anionic moiety of an acid.

- 2) Didecyl allyl methyl ammonium bromide.
- 3) Didecyl allyl methyl ammonium chloride.
- 4) Didecyl allyl methyl ammonium methosulphate.
- 5) Didecyl dimethyl-allyl methyl ammonium bromide.
- 6) Didecyl propargyl methyl ammonium bromide.
- 7) Didecyl diallyl ammonium bromide.
- 8) Didecyl dipropargyl ammonium bromide.
- 9) Didecyl allyl propargyl ammonium bromide.
- 10) Didecyl hydroxy-ethyl methyl ammonium bromide.
- 11) Didecyl methoxy-ethyl methyl ammonium bromide.
- 12) Didecyl methoxy-butyl methyl ammonium bromide.
- 13) Didecyl carbethoxy-methyl methyl ammonium bromide.
- 14) A pharmaceutical preparation comprising a quaternary ammonium compound as set forth in claim 1 in association with a compatible pharmaceutical carrier.
- 15) A process for the manufacture of the quaternary ammonium compounds claimed in

claim 1, which process comprises quaternising a tertiary amine of the formula



with a compound of the formula R^4-X

in which formulae R^1 , R^2 , R^3 , R^4 and X have the significance given in claim 1.

- 16) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents an allyl group.

- 17) A process as set forth in claim 16, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents an allyl group and another substituent represents the methyl group.

- 18) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a hydroxy-ethyl group.

- 19) A process as set forth in claim 18, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a hydroxy-ethyl group and another represents the methyl group.

- 20) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a methoxy-ethyl group.

- 21) A process as set forth in claim 20, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a methoxy-ethyl group and another represents the methyl group.

- 22) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a carbethoxy-methyl group.

- 23) A process as set forth in claim 22, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a methyl group.

- 24) A process as set forth in any one of claims 15 to 23, wherein R^4 represents a lower-alkenyl, lower-alkynyl, lower hydroxy-alkyl, lower alkoxy-alkyl, lower carboxy-alkyl or lower carbalkoxy-alkyl group.

- 25) A process as set forth in any one of claims 15 to 24, wherein X represents bromine.

- 26) A process for the manufacture of the quaternary ammonium compounds set forth in claim 1, substantially as described with reference to Examples 1 to 12.

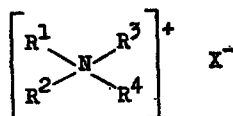
- 27) Quaternary ammonium compounds as set forth in claim 1, when manufactured by the process claimed in any one of claims 15 to 26 inclusive.

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glycerine. The aqueous solution of the active material was then added to the mixture of silicic acid and glycerine and homogenized with the aid of a homogenizer. A finely sieved mixture of the titanium dioxide and talc was added portionwise to this mixture. Homogenization was effected after each added portion by means of a homogenizer so that a fine, lump-free salve was formed. After replacement of evaporated water, the finished salve was filled into tubes which were immediately closed.

WHAT WE CLAIM IS:—

- 1) A quaternary ammonium compound of the formula



wherein two of the substituents R^1 , R^2 , R^3 and R^4 represent decyl groups, another of the substituents represents a lower-alkenyl, lower-alkynyl, lower hydroxy-alkyl, lower alkoxy-alkyl, lower carboxy-alkyl or lower carbalkoxy-alkyl, the other substituent represents a lower-alkyl, lower-alkenyl or lower-alkynyl group and X represents the anionic moiety of an acid.

- 2) Didecyl allyl methyl ammonium bromide.
- 3) Didecyl allyl methyl ammonium chloride.
- 4) Didecyl allyl methyl ammonium methosulphate.

- 5) Didecyl dimethyl-allyl methyl ammonium bromide.

- 6) Didecyl propargyl methyl ammonium bromide.

- 7) Didecyl diallyl ammonium bromide.

- 8) Didecyl dipropargyl ammonium bromide.

- 9) Didecyl allyl propargyl ammonium bromide.

- 10) Didecyl hydroxy-ethyl methyl ammonium bromide.

- 11) Didecyl methoxy-ethyl methyl ammonium bromide.

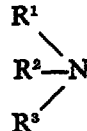
- 12) Didecyl methoxy-butyl methyl ammonium bromide.

- 13) Didecyl carbethoxy-methyl methyl ammonium bromide.

- 14) A pharmaceutical preparation comprising a quaternary ammonium compound as set forth in claim 1 in association with a compatible pharmaceutical carrier.

- 15) A process for the manufacture of the quaternary ammonium compounds claimed in

claim 1, which process comprises quaternising a tertiary amine of the formula



with a compound of the formula



in which formulae R^1 , R^2 , R^3 , R^4 and X have the significance given in claim 1.

- 16) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents an allyl group.

- 17) A process as set forth in claim 16, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents an allyl group and another substituent represents the methyl group.

- 18) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a hydroxy-ethyl group.

- 19) A process as set forth in claim 18, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a hydroxy-ethyl group and another represents the methyl group.

- 20) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a methoxy-ethyl group.

- 21) A process as set forth in claim 20, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a methoxy-ethyl group and another represents the methyl group.

- 22) A process as set forth in claim 15, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a carbethoxy-methyl group.

- 23) A process as set forth in claim 22, wherein one of the substituents R^1 , R^2 , R^3 and R^4 represents a methyl group.

- 24) A process as set forth in any one of claims 15 to 23, wherein R^4 represents a lower-alkenyl, lower-alkynyl, lower hydroxy-alkyl, lower alkoxy-alkyl, lower carboxy-alkyl or lower carbalkoxy-alkyl group.

- 25) A process as set forth in any one of claims 15 to 24, wherein X represents bromine.

- 26) A process for the manufacture of the quaternary ammonium compounds set forth in claim 1, substantially as described with reference to Examples 1 to 12.

- 27) Quaternary ammonium compounds as set forth in claim 1, when manufactured by the process claimed in any one of claims 15 to 26 inclusive.

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