

PATENT SPECIFICATION

NO DRAWINGS

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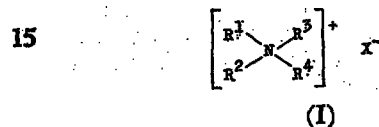
COMPLETE SPECIFICATION

Novel Quaternary Ammonium Compounds and a process for the manufacture thereof

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 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:



wherein one of the symbols R^1 , R^2 , R^3 and R^4 represents a tetradecyl group, another symbol represents an allyl group or an allyl group which is substituted by lower-alkyl, the remaining two symbols represent lower-alkyl groups and X represents the anionic moiety of an acid.

The novel quaternary ammonium compounds of 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 toxic to yeasts such as *Candida albicans*, to mould fungi such as *Aspergillus fumigatus* and to bacteria such as *Streptococci*, *Staphylococci*, *Coli* and *Pyocyanous*. As can be seen from the foregoing, they exhibit a broad antimicrobial spectrum. Since foot mycosis can be codependent on yeast and bacteria, they are especially suitable for this

indication. The novel quaternary ammonium compounds of this invention are accordingly useful 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, polyalkylene glycols and petroleum jelly. The pharmaceutical preparations can be submitted in powder form or in liquid form; for example as solutions, suspensions, emulsions or aerosols. They may contain additives such as preserving, stabilizing, wetting or emulsifying agents or buffers. They can also contain other therapeutically valuable materials. Suitably, the preparations contain from about 0.2% to 5% of the quaternary ammonium compound.

The term "lower alkyl" is used in this description and in the accompanying claims to denote straight- or branched-chain alkyl groups containing from one to seven carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). Methyl and ethyl are the preferred lower-alkyl groups. The allyl groups which are substituted by lower-alkyl are, for example, monomethyl-allyl, diethyl-allyl, methyl-isopropyl-allyl. The anionic moiety denoted by X can be the anion of any of the usual organic or inorganic acids; for example, the chloride, bromide or iodide anion 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 chlorides, bromides and methane-sulphates are especially preferred.

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

[Price 4s. 6d.]



(II)

with a compound of the formula



(III)

5 , 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 in the usual way by the introduction of the desired groups into primary or secondary amines.

10 In carrying out the quaternization, it is preferred to use the tertiary amine of formula II and the compound of formula III in approximately equimolar amounts. The quaternization is conveniently effected in the presence of an inert solvent (e.g. acetone, alcohol, ethyl acetate, N,N - dimethyl - formamide or petroleum ether). The temperature is not critical although it is preferred to operate at an elevated temperature, suitably at a temperature within the approximate range of from 50°C to 130°C.

20 In a preferred embodiment the quaternization is carried out using a compound of formula III wherein the symbol R^4 is the allyl group or an allyl group which is substituted by lower-alkyl.

25 The following Examples illustrate the process provided by the invention.

30 EXAMPLE 1

100 g of tetradecyl dimethyl amine were dissolved in 500 ml of petroleum ether (boiling range 40°—45°C) and the solution was treated with 55 g of allyl bromide. The mixture was boiled under reflux for 5 hours and then allowed to stand overnight. On the next day, the white paste which formed was filtered off, rinsed with petroleum ether and dried *in vacuo* over phosphorous pentoxide. Tetradecyl allyl dimethyl ammonium bromide was obtained as a white hygroscopic powder of melting point 61°—63°C.

EXAMPLE 2

45 100 g of tetradecyl dimethyl amine were dissolved in 300 ml of acetone and the solution was treated with 40 g of allyl chloride. The mixture was heated under reflux for 5 hours, after which time the solvent was distilled off. The solid residue was triturated with petroleum ether and the slurry was filtered. The filter cake was rinsed with petroleum ether and dried *in vacuo* over phosphorous pentoxide. Tetradecyl allyl dimethyl ammonium chloride was obtained as a white, hygroscopic powder of melting point 144°—147°C.

EXAMPLE 3

100 g of tetradecyl diethyl amine were dissolved in 300 ml of acetone and the solution was treated with 50 g of allyl bromide. The mixture was heated under reflux for 8 hours, after which time the acetone was evaporated. The residue was dissolved in 500 ml of 80% aqueous methanol and the solution was extracted with three 200 ml portions of petroleum ether (boiling range 40°—45°C). The methanol solution was evaporated *in vacuo* and the residue was dried *in vacuo*. Tetradecyl allyl diethyl ammonium bromide was obtained as a light grey hygroscopic powder of melting point 63°—66°C.

EXAMPLE 4

100 g of tetradecyl dimethyl amine were dissolved in 400 ml of acetone and the solution was treated with 70 g of dimethyl-allyl bromide. The mixture was heated under reflux for 5 hours, after which time the solvent was evaporated. The residue was dissolved in 500 ml of 80% aqueous methanol and the solution was extracted with three 200 ml portions of petroleum ether (boiling range 40°—45°C). The methanol solution was evaporated and the residue was dried *in vacuo*. Tetradecyl dimethyl-allyl dimethyl ammonium bromide was obtained as a light grey hygroscopic powder of melting point 58°—60°C.

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

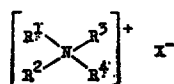
A) A paste containing 2.0 g of tetradecyl allyl dimethyl ammonium bromide, 3.0 g of titanium dioxide, 2.0 g of deodorized lanolin, 3.0 g of yellow petroleum jelly, 6.0 g of stearin, 6.0 g of cetyl alcohol, 5.0 g of polyoxyethylene-sorbitan monostearate and distilled water to 100 g was prepared by melting together the deodorized lanolin, yellow petroleum jelly, stearin, cetyl alcohol and polyoxyethylene-sorbitan monostearate on a steam-bath, adding the hot water *ca* 75°C to the hot melt (*ca* 70°—75°C) in a spray, stirring the mixture at room temperature (evaporated water being continuously replaced with distilled water), gradually admixing with the ointment base thus obtained a mixture of the finely sieved active material and the finely sieved titanium dioxide (care being taken that the latter mixture was well ground and the ointment base and finely divided therein) and evaporated water was replaced.

B) A salve containing 1 g of tetradecyl allyl dimethyl ammonium bromide, 4 g of silicic acid, 20 g of titanium dioxide, 20 g of talc, 20 g of glycerin (pure) and distilled water to 100 g was prepared by working up the

- silicic acid to a homogeneous mixture in a mortar at room temperature, by means of a homogenizer, mixing the homogenate with the glycerin, adding to the mixture a solution obtained by dissolving the active material in about one quarter of the water at *ca* 50°C, homogenizing with the aid of a homogenizer, adding a finely sieved mixture of the titanium dioxide and the talc in portions (homogenizing after each added portion by means of a homogenizer, so that there was formed a fine, lump-free salve) and replacing evaporated water; the finished salve was filled into tubes which were immediately closed.

WHAT WE CLAIM IS:—

1. Quaternary ammonium compounds of the formula



- 20 wherein one of the symbols R^1 , R^2 , R^3 and R^4 represents a tetradecyl group, another symbol represents an allyl group or an allyl group which is substituted by lower-alkyl, the remaining two symbols represent lower-alkyl groups and X represents the anionic moiety of an acid.
2. Tetradecyl allyl dimethyl ammonium bromide.
3. Tetradecyl allyl diethyl ammonium bromide.
- 30 4. Tetradecyl allyl dimethyl ammonium chloride.
5. Tetradecyl dimethyl-allyl dimethyl ammonium bromide.
- 35 6. A pharmaceutical preparation comprising a quaternary ammonium compound as claimed in claim 1 in association with a compatible pharmaceutical carrier.

7. A process for the manufacture of the quaternary ammonium compounds claimed in claim 1, which process comprises 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 in claim 1.

8. A process as set forth in claim 7, wherein one of the symbols R^1 , R^2 , R^3 and R^4 represents an allyl group.

9. A process as set forth in claim 8, wherein two of the symbols R^1 , R^2 , R^3 and R^4 represent methyl groups.

10. A process as set forth in claim 7, claim 8 or claim 9, wherein the symbol R^4 represents an allyl group.

11. A process as set forth in any one of claims 7 and 10 inclusive, wherein X represents bromine.

12. A process as set forth in claim 7, wherein tetradecyl dimethyl amine is quaternized with allyl bromide.

13. A process for the manufacture of the quaternary ammonium compounds set forth in claim 1, substantially as described with reference to Examples 1 to 4.

14. Quaternary ammonium compounds as claimed in claim 1, when manufactured by the process claimed in any one of claims 7 to 13 inclusive.

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Patent Agent,

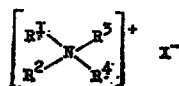
for F. Hoffmann-La Roche & Co.,
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- 5 silicic acid to a homogeneous mixture in a mortar at room temperature, by means of a homogenizer, mixing the homogenate with the glycerin, adding to the mixture a solution obtained by dissolving the active material in about one quarter of the water at *ca* 50°C, homogenizing with the aid of a homogenizer, adding a finely sieved mixture of the titanium dioxide and the talc in portions (homogenizing after each added portion by means of a homogenizer, so that there was formed a fine, lump-free salve) and replacing evaporated water; the finished salve was filled into tubes which were immediately closed.

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1. Quaternary ammonium compounds of the formula



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3. Tetradecyl allyl diethyl ammonium bromide.
4. Tetradecyl allyl dimethyl ammonium chloride.
5. Tetradecyl dimethyl-allyl dimethyl ammonium bromide.
- 35 6. A pharmaceutical preparation comprising a quaternary ammonium compound as claimed in claim 1 in association with a compatible pharmaceutical carrier.

7. A process for the manufacture of the quaternary ammonium compounds claimed in claim 1, which process comprises 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 in claim 1.

8. A process as set forth in claim 7, wherein one of the symbols R^1 , R^2 , R^3 and R^4 represents an allyl group.

9. A process as set forth in claim 8, wherein two of the symbols R^1 , R^2 , R^3 and R^4 represent methyl groups.

10. A process as set forth in claim 7, claim 8 or claim 9, wherein the symbol R^4 represents an allyl group.

11. A process as set forth in any one of claims 7 and 10 inclusive, wherein X represents bromine.

12. A process as set forth in claim 7, wherein tetradecyl dimethyl amine is quaternized with allyl bromide.

13. A process for the manufacture of the quaternary ammonium compounds set forth in claim 1, substantially as described with reference to Examples 1 to 4.

14. Quaternary ammonium compounds as claimed in claim 1, when manufactured by the process claimed in any one of claims 7 to 13 inclusive.

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