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TOPICAL PHARMACEUTICAL COMPOSITION
COMPRISING CERTAIN QUATERNARY AM-
MONIUM COMPOUNDS

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No Drawing. Filed Apr. 8, 1968, Ser. No. 719,668
Claims priority, application Sweden, Apr. 6, 1967, 4,899/67

Int. Cl. A61k 27/00

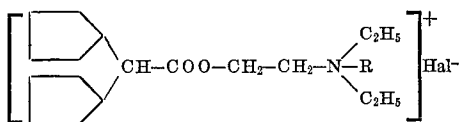
U.S. Cl. 424—311

7 Claims

ABSTRACT OF THE DISCLOSURE

An antimicrobial pharmaceutical composition in particular for dermatological purposes and a method of treating with such pharmaceutical compositions infections of the skin and mucous membranes of animals and particularly human beings, the said pharmaceutical compositions containing as an essential ingredient a quaternary ammonium compound of dicyclopentylacetic acid diethylaminoethyl ester with an alkyl halide having from 5 to 12 and particularly 6 to 10 and most preferably 8 carbon atoms.

This invention relates to a new and useful pharmaceutical composition, and more particularly to an antimicrobial pharmaceutical composition containing as an active ingredient at least one quaternary ammonium compound having the general formula



wherein R is an alkyl radical having from 5 to 12 carbon atoms and "Hal" is a halogen atom.

Quaternary ammonium salts of diethylamino ethyl esters of dicyclopentylacetic acid have been described e.g. in the British Patent 893,163 as showing a high spasmolytic activity. While optimum spasmolytic effects were observed on quaternary salts of the said basic ester with lower alkyl halides having only a few and preferably two carbon atoms, it has now surprisingly been found that quaternary salts of the same basic ester with alkyl halides having from 5 to 12 and preferably from 6 to 10 carbon atoms and most preferably 8 carbon atoms, exhibit an outstanding antimicrobial activity.

In microbiological tests the quaternary compounds as defined above show in particular a broad activity spectrum against gram-positive and gram-negative bacteria, pathogenic fungi such as yeasts and dermatophyta, and selected protozoa.

The following table comprises some results obtained with a number of quaternary compounds as defined above against nine representative pathogenic bacteria and fungi, namely:

- A—*Staphylococcus aureus*
B—*Escherichia coli*
C—*Proteus vulgaris*
D—*Pseudomonas pyocyanea*
E—*Streptococcus faecalis*
F—*Candida albicans*
G—*Aspergillus niger*
H—*Trichophyton mentagrophytes*
J—*Mycobacterium tuberculosis* (Typus humanus)

In the table to figures of the columns A–H refer to the width (mm.) of the zones of inhibition around a circu-

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lar hole of 8 mm. diameter in the inoculated agar culture medium filled with an aqueous solution (1:1000) of the test compound. The figures of column J refers to the tuberculo-static effect determined by dilution series in Dubos medium.

In order to compare the activities of the compound with prior art, the last line ("Comparison") shows the corresponding results determined with benzalkonium chloride which is a disinfectant known for high antimicrobial activity.

Compound of Formula I	R	X	Antimicrobial activity								
			A	B	C	D	E	F	G	H	J
15	C ₅ H ₁₁ ----	Br	17.3	0.5	0	0	4.3	3.4	0	0	4.3
	C ₆ H ₁₃ ----	Br	21.2	2.8	0	1.1	9.1	9.8	2.2	1.8	5.0
	C ₇ H ₁₅ ----	Br	21.1	6.8	0	2.1	12.3	12.9	3.7	20.7	5.0
	C ₈ H ₁₇ ----	Br	17.2	6.9	2.3	3.0	10.0	14.9	3.4	24.6	5.0
	C ₉ H ₁₉ ----	I	18.2	8.5	0	2.8	11.8	17.2	2.4	27.2	-----
	C ₁₀ H ₂₁ ----	Br	12.7	6.6	1.6	3.4	8.3	12.3	1.0	11.5	4.3
	C ₁₁ H ₂₃ ----	Br	9.0	4.2	1.5	1.8	5.6	9.9	3.6	11.7	-----
	C ₁₂ H ₂₅ ----	Br	5.7	2.4	1.3	1.0	2.9	5.8	3.4	7.7	-----
20	C ₁₂ H ₂₅ ----	Br	3.5	0.7	0	0	1.4	2.2	1.0	4.7	4.0
	Comparison		13.4	3.6	0	0.9	5.2	14.0	0	11.3	4.7

Furthermore the fungistatic activities of our compounds were determined by dilution series against *Candida albicans* which is an important pathogenic yeast fungus. By this test it could be shown that minimal concentration for inhibiting growth of the said fungus is for example in the case of dicyclopentylacetic acid diethylaminoethyl ester octobromide only 25 mg./liter whereas the minimum inhibitory concentration of salicylanilide is 500 mg./liter and that of undecylenic acid as well as of butyl p-hydroxy-benzoate is 250 mg./liter. Thus, the antimicrobial potency of our compounds is remarkably higher as compared with representative disinfectants of prior art.

In addition, the acute toxicity of our compounds is low. For example, on mice the above mentioned octobromide exhibits a DL₅₀ value (peroral) of 900 mg./kg. Pharmacological tests showed no percutaneous absorption in the rats tail-test even when using high concentrations, and no irritation was found due to the said octobromide on application of 1% solution on the intact rabbit skin or 0.1% ointment on the intact human skin. Sensibilization in guinea pigs could not be observed.

For clinical examination a 0.1% ointment of the said octabromide was used for treatment of 295 patients exhibiting symptoms of inguinal mycosis, acute or subacute epidermaphytosis, superinfected mycotic eczema, mycoid or intertriginous or parasitic eczema. In 228 cases good or very good results were obtained; irritations and other undesirable side effects were not observed.

Thus, our compounds have been proved to be dermatotherapeutica which are superior to other non-corticoid remedies for the same indication, and pharmaceutical compositions containing quaternary compounds of the dicyclopentylacetic acid diethylaminoethyl ester with alkylhalides having 5 to 12 carbon atoms and a suitable vehicle are valuable remedies for the treatment of infectious diseases of the skin and mucous membranes of animals and human beings such as itching and allergic dermatosis, dermatitis, eczema, dermato-mycosis, and other kinds of bacterial skin diseases.

The pharmaceutical compositions of the invention can be ointments, soft pastes, creams, jellies, powders, solutions, suspensions, emulsions, lotions or any other formulations known to the man skilled in the art. Thus, any suitable vehicle or carrier may be used for the preparation of the pharmaceutical compositions of the invention, such as oil/water emulsions, water/oil emulsions, fatty bases, polyethylene glycol bases, silicone bases, starches, isopropanol, talcum, silicium dioxide etc. In addition, the pharmaceutical compounds may contain other active ingredients for dermatological purposes such as diphen-

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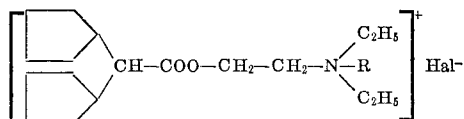
hydramine hydrochloride, 8-hydroxyquinoline salicylate, anti-inflammatory steroids etc.

A typical pharmaceutical composition according to the present invention in the form of an ointment may be prepared by admixture of 1 part dicyclopentylacetic acid diethylaminoethyl ester octobromide, 60 parts polyethylene glycol 400 and 40 parts of polyethylene glycol 4000, and a powder may be prepared by blending 1 part of the said active ingredient with 100 parts of talcum.

The quaternary ammonium compounds as defined above may be prepared by methods known in the art, for example according to the method described in the British Patent No. 893,163 by condensing dicyclopentylacetic acid chloride with diethylaminoethanol followed by reaction of the so obtained ester with the desired alkylhalide.

We claim:

1. A topical pharmaceutical composition for inhibiting growth of pathogenic fungi and bacteria on the skin and mucous membranes of animals and human beings, comprising a pharmaceutically acceptable topical carrier selected from the group consisting of ointment, paste, cream, jelly, starch, talcum and silicon dioxide; and an effective amount of quaternary ammonium compound having the formula



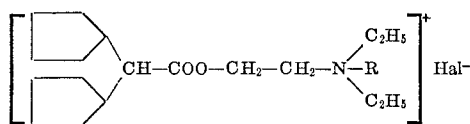
wherein R is alkyl having from 5 to 12 carbon atoms and Hal is halogen.

2. A topical pharmaceutical composition according to claim 1, wherein R is alkyl having from 6 to 10 carbon atoms.

3. A topical pharmaceutical composition according to claim 2, wherein said quaternary ammonium compound is dicyclopentylacetic acid diethylaminoethyl ester octobromide.

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4. A method of inhibiting growth of pathogenic fungi and bacteria on the skin and mucous membranes of animals and human beings comprising topically administering to said animals and human beings in need of said treatment an effective dose of a quaternary ammonium compound having the formula



wherein R is alkyl having from 5 to 12 carbon atoms and Hal is halogen.

5. A method according to claim 4, wherein R is alkyl having from 6 to 10 carbon atoms.

6. A method according to claim 4, wherein said compound is administered with a pharmaceutically acceptable topical carrier.

7. A method according to claim 4, wherein said compound is dicyclopentylacetic acid diethylaminoethyl ester octobromide.

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U.S. Cl. X.R.

424—329