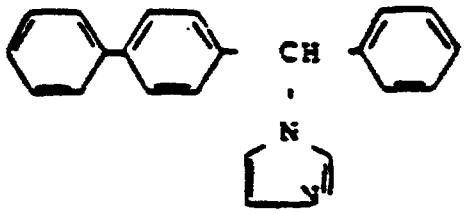
ANTIMYCOTIC AGENT WITH A HIGH RELEASE OF ACTIVE COMPOUNDS, IN THE FORM OF A CREAM

The present invention relates to a novel formulation of the known atimycotic compound bifonazole of the formula



which has a relatively high release of the active compound and thereby permits short-term therapy.

Formulations of antimycotic derivatives have already been disclosed for the treatment of mycoses in humans, above all mycoses of the skin and cutaneous appendages. A therapy time of 14 to 21 days has been required for complete cure with these formulations.

In order to shorten the duration of therapy, for example in the case of vaginal or buccal mycoses or dermatomycoses, higher release of the active compounds in an aqueous medium is necessary, in particular to eliminate the germs and to achieve a mycologically reliable cure. The known formulations are of only limited suitability for this, because only a small amount of the active compound available dissolves in the volume of liquid at the infection site. Thus, if a shortening in the duration of therapy, for example to a few days with a single daily administration, is to be achieved, with or without a further increase in the concentration of active compound, optimum bioavailability of the active compound must be ensured.

It has now been found that certain formulations of bifonazole which contain spreading agents, in addition to conventional formulation auxiliaries and solvents, release a greater amount of the active compound and thereby permit

(10)

a shortening of the duration of therapy to a few days. This effect of higher release of active compound can achieve an increase up to a power of ten.

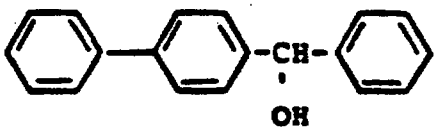
The invention provides a high release antimycotic composition comprising, by weight 0.5-1.5% of bifonazole, 1-3% of sorbitan monostearate, 0.5-2.5% of polyoxyethylene (20)-sorbitan monostearate, 2-4% of synthetic spermacetic (cetyl palmitate), 5-15% of cetyl-stearyl alcohol, 5-25% of 2-octyldodecanol, 0.5-1.5% of benzyl alcohol, and demineralised water to make up 100%.

The cetyl-stearyl alcohol and the 2-octyldodecanol are spreading agents.

Spreading agents are understood as meaning oily liquids which distribute themselves particularly readily on the skin (R.Keymer, Pharm. Ind. 32 (1970) 577-581).

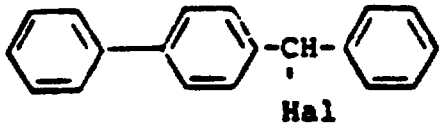
The formulations according to the invention may be prepared by a process in which, in a manner which is known per se, either

(a) the carbinol of the formula



is reacted with thionyl-bis-imidazole, if appropriate in the presence of a diluent, or

(b) the halogeno-methane of the formula



or

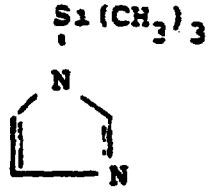
(11)

is either

1) reacted with imidazole, if appropriate in the presence of an acid-binding agent and if appropriate in the presence of a diluent, or

2) reacted with the silver salt or alkali metal salts of the imidazole, if appropriate in the presence of a diluent, or

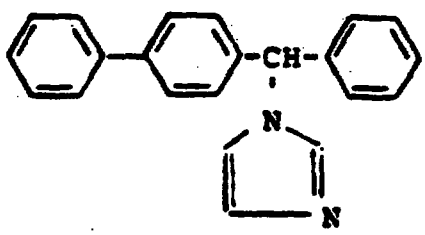
3) reacted with trimethylsilylimidazole of the formula



if appropriate in the presence of a diluent, and, if appropriate, the azol-1-ly-methane thereby obtained is reacted with physiologically acceptable acids, and the product thereby obtained is mixed with the other ingredients of the formulation.

An oil-in-water cream may conveniently be made from the above ingredients in three phases. In Phase I, the sorbitan monostearate, the polyoxyethylene (20)-sorbitan monostearate, the synthetic spermaceti, the cetylstearly alcohol and the 2-octyldodecanol are warmed to 75° C, with stirring, to form a mixture. In Phase II, the bifonazole is added, with stirring, to form a solution. In Phase III, the benzyl alcohol and the demineralised water are warmed to 75°C and added, with intensive mixing, followed by slow cooling to room temperature, with further stirring, and homogenisation.

The composition according to the invention preferably contains bifonazole in an amount of 1%



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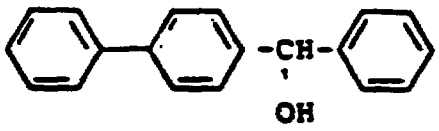
Process variant (a)

13.6 g (0.2 mole) of imidazole are dissolved in 150 ml of acetonitrile, and 3.5 ml of thionyl chloride are added at 10°C. 13 g (0.05 mole) of diphenyl-phenyl-carbinol are added to the solution of thionyl-bis-imidazole thus obtained. After the mixture has been left to stand at room temperature for 15 hours, the solvent is removed by distillation in vacuo. The residue is taken up in chloroform and the mixture is washed with water. The organic phase is separated off, dried over sodium sulphate and filtered and the solvent is distilled off in vacuo. The oily residue is dissolved in ethyl acetate and the solution is freed from insoluble, resinous constituents by filtration. The solvent is distilled off again in vacuo and the residue is purified by recrystallisation from acetonitrile. 8.7 g (56% of theory) of dipheny-imidazole-1-phenyl-methane (bifonazole) of melting point 142°C are obtained.

Starting substance



38.8 g (0.15 mole) of 4-phenyl-benzophenone are dissolved in 200 ml of ethanol, and 3 g (0.075 mole) of sodium borohydride are added. After the mixture has been heated under reflux for 15 hours, the cooled reaction mixture is hydrolysed with water containing a small amount of hydrochloric acid. The solid thereby formed is purified by recrystallisation from ethanol. 36 g (89% of theory) of diphenyl-phenyl-carbinol of melting point 72-73°C are obtained.

Process variant (b/3.)

167 g (0.6 mole) of diphenyl-phenyl-chloro-methane and 92 g (0.66 mole) of trimethylsilylimidazole, dissolved in 500 ml of acetonitrile, are heated under reflux for 15 hours. After the solvent has been distilled off, the

(13)

crystalline residue is purified by recrystallisation from ethyl acetate. 97 g (52% of theory)of diphenyl-imidazol-1-yl-phenyl-methane (bifonazole) of melting point 142°C are obtained.

The following example illustrates the invention.

Example 1 **Cream,oil-in-water**

Phase 1	
Sorbitan monostearate	2.0g
Polyoxyethylene (20)-sorbitan monostearate	1.5g
Synthetic spermaceti	3.0g
Cetyl-stearyl alcohol	10.0g
2-Octyldodecanol	13.5g
Warm to 75°C, stir,mix.	
Phase II	
Bifonazole	1.0g
Add to phase I, stir,dissolve.	
Phase III	
Benzyl alcohol	1.0g
Water,demineralised	68.0g

Warm to 75°C and add to phase II. Mix intensively, cool slowly to room temperature, with further stirring. Homogenise.

Testing of the activity of the agents according to the invention of guinea pigs infected with Trichophyton

Trichophyton-infected Pirbright white guinea pigs weighing on average 600 g were used as the test model for comparative testing of the activity of the formulations according to the invention. The backs of the animals were shaved with electric clippers such that stubble about 1/10mm long remained.

(14)

The animals were infected with Trichophyton mentagrophytes by gently rubbing a spore suspension, which had been germinated in Sabouraud nutrient solution for 24 hours, of the pathogen on an approximately 2 x 2 cm area of their shaved backs. 0.5 ml of germ suspension containing 1-3 x 10^5 infectious fungal particles, was applied per animal.

With this mode of infection, the first symptoms of dermatophytosis manifest themselves as reddening and scaling of the skin 2-3 days after infection. In the case of untreated animals, the dermatophytosis is of maximum severity about 14 days after infection: areas of hair loss and bloody integumentary defects within a scaly edge zone changed by inflammation.

The formulations to be tested were applied locally to the reddened infection site of the animals once, on the 2nd day after infection, and were gently rubbed in with a horn spatula. In each case 0.5 ml of the formulations = 5 mg of active compound (1% strength formulation) was applied. The progress of the infection was evaluated daily up to the 20th day after infection.

The formulations according to the invention exhibit a very good action in this test.

If formulations which, besides bifonazole, contain no spreading agent are used for comparison, an effect corresponding to that of the formulations according to the invention is achieved only after three applications.

It will of course be understood that the present invention has been described above purely by way of example, and modifications of detail can be made within the scope of the invention.

(15)

Claims

1. A high release antimycotic composition comprising, by weight 0.5 - 1.5% of bifonazole, 1-3% of sorbitan monostearate, 0.5-2.5% of polyoxyethylene (20)-sorbitan monostearate, 2-4% of synthetic spermaceti (cetyl palmitate), 5-15% of cetyl-stearyl alcohol, 5-25% of 2-octyldodecanol, 0.5-1.5% of benzyl alcohol, and demineralised water to make up 100%.

2. An antimycotic composition according to claim 1 which contains 1.0% of bifonazole.

3. An antimycotic composition according to claim 1, substantially as described in Example 1.

4. An antimycotic composition according to claim 1 for use in combating mycoses.

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