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ANESTHETIC AND FUNGICIDAL CHLOROTHYMOL COMPOSITION AND SOLUTION THEREOF

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This invention relates to a novel composition in the form of a liquid preparation of germicidal detergent and deodorant properties adapted for topical application which is in addition particularly and unexpectedly effective as a fungicide, local anesthetic and the like.

The individual components of the composition of our invention are well known materials which, however, when brought together in admixture appear to co-act in some unexplained manner to impart certain unusual and unexpected properties to the mixture, over and above the expected, known, properties of the individual components, such as germicidal deodorizing and detergent actions. The effect of this phenomenon, which appears to be synergistic in character, is reflected most clearly and dramatically in the fungicidal and anesthetic properties of our composition, and will be pointed out in more detail as the description of our invention proceeds.

The unusual anesthetic qualities of our composition appear to be due to the co-presence of certain non-ionic surface active agents with a quaternary ammonium compound, with a solvent for these materials. In this connection we have discovered that not only do these non-ionic surface active agents have a significant anesthetic character in themselves, but that this property is potentiated or synergized when a quaternary ammonium compound is present in solution therewith.

The addition of an organic fungicide to the above mixture results in supplementing the unexpected anesthetic property of the mixture with a similarly unexpected increase in fungicidal effectiveness as will be pointed out hereinafter.

While a preferred form of our composition includes materials which contribute pharmaceutical elegance thereto, and which have some contributing effect to the overall efficiency thereof, such as essential oils, camphor, menthol and like materials, the unexpected anesthetic and the fungicidal properties are due primarily to the co-presence of materials hereinbefore mentioned, i. e., certain non-ionic surface active agents, quaternary ammonium compounds and organic fungicides.

Generally speaking the composition of our invention consists of about 6 to 40 parts by weight

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of quaternary ammonium compound, 5 to 40 parts by weight of non-ionic surface active agent, and 1 to 4 parts by weight of an organic fungicide, the whole dissolved for use in an aqueous vehicle, such as water itself, or water to which has been added other solvents such as ethyl alcohol, propylene glycol, and the like. The primary ingredients are soluble in water alone, the organic fungicide being solubilized by the non-ionic surface active agent and the quaternary ammonium compound. But where additional water insoluble ingredients are desired such as essential oils, camphor, menthol and the like, it may be necessary to add solvents such as the glycols and alcohols to produce a clear solution.

The composition may be prepared either with or without the aqueous vehicle with instructions to the user to dilute it suitably. For use on human skin as a local anesthetic or fungicide, it is preferred that sufficient aqueous vehicle should be present to bring the active ingredients within the following ranges: About 0.3 to 2.0% of quaternary ammonium compound; 0.25 to 2.0% of non-ionic surface active agent; 0.05 to 0.20% of an organic fungicide.

Any quaternary ammonium compound may be used including such compounds as: alkylaryl-ether dimethyl benzyl ammonium chloride, an example of which is di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride available under the name of "Hyamine 10X"; alkyl dimethyl benzyl ammonium chloride, such as the product known as "Benzalkonium"; alkyl trimethyl ammonium chloride, such as cetyl trimethyl ammonium chloride available under the name of "Cetab"; alkyl dimethyl ethyl ammonium halide such as alkenyl dimethyl ethyl ammonium bromide known under the trade name of "Onyxide"; alkyl pyridinium chloride, such as cetyl pyridinium chloride; alkyl imidazolinium chloride such as alkyl hydroxyethyl imidazolinium chloride known as Alrosept MB; alkyl dimethyl dichlorobenzyl ammonium chloride such as alkyl dimethyl 3:4 dichloro-benzyl ammonium chloride known as "Tetrosan"; acyl colamino alkyl pyridinium chloride such as acylcolamino formyl methyl pyridinium chloride available under the name of Emulsept; and alkaryl methyl pyridinium chloride such as polyalkyl naph-

thalene methyl pyridinium chloride available under the trade name of "Emcol." In these compounds the "alkyl" is understood to be from C_8H_{17} to $C_{18}H_{37}$ including mixtures within this range, this being the range in which quaternary ammonium compounds are considered to have good germicidal activity.

Among the non-ionic surface active agents which we may use are the following: alkylaryl polyethylene glycols (including alkylated aryl polyether alcohol, mono or dimeric) such as the product known as "Antarox A400," and such as polyethylene glycol mono-iso-octyl phenyl ether, available under the trade name of "Triton X-100"; alkyl polyoxyethylene alcohol such as the product known as "Cerfak 1300"; and amides and amide ethers of fatty acids such as the secondary amide of lauric acid known as "Drew 1011," and the higher fatty acid amide known as "Miragene T."

Example I

Di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride	grams	0.50
Polyethylene glycol mono-iso-octyl phenyl ether	grams	0.35
Chlorothymol	do	0.10
Menthol	do	0.10
Camphor	do	0.10
Alcohol (as absolute alcohol)	milliliters	4.0
Propylene glycol	do	6.25
Essential oils	grams	0.10
Water, a sufficient quantity to make 100 milliliters.		

Alternatively this composition may be prepared in more concentrated form without some or all of the water or alcohol, the remaining ingredients being mutually soluble, such concentrate to be suitably diluted with water by the user. The concentrate is miscible with water in all proportions. The proportion of water cited in the example is the preferred amount when the product is to be used for its local anesthetic or fungicidal actions on human skin. This proportion of water is also suitable when the product is used as a germicide on skin or in wounds, but for deodorant or detergent use the product can be further diluted with water if desired.

As indicated heretofore one of the important and unexpected properties of this composition is its anesthetic property. This is reflected in the considerable amount of local anesthesia which is manifested when the composition is applied as an antipruritic to the skin for the relief of itching, irritation, or stinging caused by various skin diseases or disorders, burns or insect bites. This property has been demonstrated not only clinically on human patients, but also by means of test procedures using a corneal test with rabbits as the test animals.

In this test, the rabbits were placed in upright position in stocks, and about 3 to 4 rabbits were tested at one time. All of the corneas were stimulated with a horse hair, using uniform pressure, 5 consecutive times at about 2 second intervals, the number of wink reflexes per 5 stimulations being recorded. Only rabbits which responded 5 times per 5 stimulations were used for testing. After the test animals were graded and selected in this way, the test solutions were introduced by means of a medicine dropper, 5 drops per eye into the conjunctival sac. The stimulæ were applied after 1 minute, 2 minutes, and then at 2 minute intervals for 20 minutes. The stimulæ were then

applied at 5 minute intervals until the responses were normal.

Table A illustrates the effectiveness of a 10% solution of the composition of Example 1 (which corresponds to a 0.035% concentration of the non-ionic surface active agent and a 0.05% concentration of the quaternary ammonium compound), in comparison with solutions of 0.5% butyn sulfate, 0.5% procaine hydrochloride, and 0.1% cocaine hydrochloride, respectively, when tested in accordance with the foregoing test procedure.

Table A

Time (min.)	*A	*B	*C	"Eye Number" *D
0	5.0	5.0	5.0	5.0
1	2.2	5.0	5.0	5.0
2	1.2	5.0	4.8	5.0
4	1.1	3.8	3.4	4.6
6	1.1	1.9	2.4	3.8
8	0.9	1.4	1.6	3.2
10	1.3	1.0	1.0	2.4
12	1.9	0.9	0.6	1.8
14	2.1	1.6	0.8	1.6
16	2.8	2.1	1.2	1.8
18	3.4	3.1	1.8	1.0
20	3.8	3.6	3.2	3.0
25	4.2	4.4	4.8	4.0
30	4.8	5.0	4.8	5.0

*A—10% solution of the composition of Example 1.

*B—0.5% solution of Butyn sulfate.

*C—0.5% solution of procaine hydrochloride.

*D—0.1% solution of cocaine hydrochloride.

The figures in each of the columns under A, B, C, and D, represent the number of wink reflexes per 5 stimulations ("eye number"), as described in the test procedure. The figures are average for a number of test animals in each case.

It will be noted that the onset of anesthesia is more rapid in the case of our composition, i. e., "A," than with the three commonly accepted local anesthetics listed. Furthermore, the peak local anesthetic effect in the case of "A" was reached in 8 minutes, but only after 12, 12 and 18 minutes with procaine hydrochloride, butyn sulphate and cocaine hydrochloride respectively.

The anesthetic properties of polyethylene glycol mono-iso-octyl phenyl ether (sold under the trade name of Triton X-100 by the Rohm and Haas Co.), di-isobutyl cresoxy ethyl dimethyl benzyl ammonium chloride (sold under the trade name of Hyamine), and the mixtures thereof are shown in Table B. The data was obtained in accordance with the same test procedure described in connection with Table A.

Table B

Time (min.)	*A	**B	***C	"Eye Number" ****D
0	5.0	5.0	5.0	5.0
1	5.0	3.5	2.9	2.2
2	5.0	2.4	1.8	1.2
4	5.0	2.2	1.5	1.1
6	5.0	2.9	1.7	1.1
8	5.0	2.6	1.7	0.9
10	4.6	2.8	2.1	1.3
12	5.0	3.7	2.1	1.9
14	5.0	4.0	2.1	2.1
16	5.0	4.1	3.0	2.8
18	5.0	4.5	3.1	3.4
20	5.0	4.5	3.4	3.8
25		4.9	3.6	4.2
30		4.7	3.7	4.8
35		5.0	4.0	5.0
40			4.8	5.0
50			5.0	

*A—A 0.5% solution of di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride, in water.

**B—A 0.035% solution of polyethylene glycol mono-iso-octyl phenylether, in water.

***C—A solution consisting of 0.05% di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride and 0.035% of polyethylene glycol mono-iso-octyl phenyl ether, in water.

****D—A 10% solution of the composition of Example I.

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From the aforesaid table, it is seen that the quaternary ammonium (A) has substantially no anesthetic effect; that the solution of the non-ionic surface active agent (B) has marked anesthetic properties; and that the mixture (C) is unexpectedly superior to either (A) or (B) alone. Mixture (D), which is a 10% solution of the preferred composition shown in Example I, is seen to have an anesthetic effect of the same order as mixture (C).

The reason for the unexpected increase in anesthetic activity of polyethylene glycol mono-iso-octyl phenyl ether, and like non-ionic substances heretofore described, in the presence of a quaternary ammonium compound is not clearly understood, but the phenomenon does occur and appears to be due to a synergistic relationship between these materials.

The following examples illustrate the local anesthetic activities of composition identical with that of Example I except that various non-ionic surface active materials were substituted, in like amount, for the polyethylene glycol mono-iso-octyl phenyl ether of Example I.

EXAMPLE II

The composition of Example I was changed by substituting, for the non-ionic surface active compound thereof, a like amount of a secondary amide of lauric acid, sold under the trade name of "Drew 1011" by the E. F. Drew Co. The local anesthetic activity of a 10% solution of this composition was determined in accordance with the procedure described in connection with Example I, with the following results:

Time (min.):	"Eye number"
0	5.0
1	5.0
2	5.0
4	4.5
6	4.0
8	3.5
10	4.5
12	4.5
14	5.0
16	4.5
18	4.5
20	5.0

EXAMPLE III

An alkylaryl polyethylene glycol, sold under the trade name of Antarox A400 was substituted in like amount for the non-ionic surface active compound of Example I, and a 10% solution of the resulting composition was tested as in Example II, with the following results:

Time (min.):	"Eye number"
0	5.0
1	5.0
2	3.0
4	3.0
6	3.0
8	3.5
10	2.5
12	4.0
14	4.5
16	5.0

EXAMPLE IV

A higher fatty acid amide ether sold under the trade name of Miragene T, was substituted, in like amount, for the non-ionic surface active compound of Example I, and a 10% solution of

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the resulting composition tested as in Example II with the following results:

Time (min.):	"Eye number"
0	5.0
1	5.0
2	4.5
4	4.5
6	4.5
8	5.0
10	4.0
12	4.5
14	4.5
16	4.5
18	4.5
20	4.5
25	4.5
30	5.0
35	5.0

EXAMPLE V

An alkyl polyoxyethylene alcohol sold under the trade name of Cerfak 1300 was substituted for the non-ionic surface active compound of Example I, and a 10% solution of the resulting composition was tested as in Example II with the following results:

Time (min.):	"Eye number"
0	5.0
1	3.5
2	4.5
4	2.5
6	3.0
8	4.0
10	4.5
12	5.0
14	5.0

Another important and unexpected quality of the composition of our invention is its superior fungicidal properties, which, on the basis of clinical tests showed it to be more effective in the treatment of ring worm infections of the type commonly referred to as "athletes foot" than would be expected from the actions of its individual components in the treatment of this infection.

Comparative in vivo tests of the composition of Example I, against a solution of 0.5% chlorothymol in a menstruum of 70 parts acetone and 30 parts water showed conclusively the more effective antifungal action of applicants' composition than those exhibited by the chlorothymol-acetone-water mixture, even though the chlorothymol concentration of the latter composition was five times as great as in our composition. Thus, our composition effected a higher incidence of fungus eradication (100% as compared to 71% for 0.5% chlorothymol-acetone-water), and furthermore, the fungicidal action was effected during shorter periods to topical application than was the case with the chlorothymol-acetone-water composition.

While the reason for the unexpected fungicidal activity of our composition is not entirely clear, it appears that the potentiation of an organic fungicide such as chlorothymol may be due in part at least to a co-action in the nature of synergism between the chlorothymol and the surface active compounds of our composition, namely, the quaternary ammonium component and the non-ionic solubilizing agent.

Another unexpected action of our composition is its anti-pruritic effect as reflected in the

marked relief afforded to the itching and discomfort concomitant to cases of "athletes foot."

In sharp contrast to the immediate relief of itching when our composition was applied to the feet, treatment with 0.1% chlorothymol in acetone resulted in immediate irritant effects, stinging, itching, or burning and subsequent signs of inflammation and/or fissures and scaling. With acetone alone, these inflammatory reactions were not experienced at all, hence the adverse effects appear to be due to the chlorothymol itself.

Hence it is clear that in the case of our composition, there is some co-action between the organic fungicide component, such as chlorothymol, and components such as the quaternary ammonium compound, the non-ionic surface active agent, and possibly some of the other components of the preferred form of our composition as described in Example I, which is responsible for the unexpected properties thereof.

The composition of our invention in its presently preferred form, has a wide range of usefulness as a topical application, including not only its unexpected local anesthetic and fungicidal efficacy, but additionally, such important attributes as the property of preventing vesicle formation following thermal or chemical trauma, highly satisfactory, non-irritating germicidal, detergent and deodorant properties, its anti-pruritic activity and others.

It is to be understood that the foregoing examples have been given by way of illustration only and should not be interpreted as limiting the appended claims except as may be required by the prior art.

We claim:

1. A composition of matter comprising di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride about 0.50 part by weight, polyethylene glycol mono-iso-octyl phenyl ether about 0.35 part by weight, chlorothymol about 0.10 part by weight, menthol about 0.10 part by weight, camphor about 0.10 part by weight, and essential oils about 0.10 part by weight.

2. A solution of the composition of claim 1, in an aqueous mixture of alcohols.

3. A composition of matter comprising di-isobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium chloride about 0.50 gram, polyethylene glycol mono-iso-octyl phenyl ether about 0.35 gram, chlorothymol about 0.10 gram, camphor about 0.10 gram, alcohol 4.0 milliliters, propylene glycol about 6.25 milliliters, essential oils about 0.10 gram, and sufficient water to make 100 milliliters.

4. A composition of matter possessing synergized anesthetic and fungicidal properties which comprises a surface active quaternary ammonium

compound, a non-ionic surface active agent, and chlorothymol.

5. A composition according to claim 4 in aqueous solution.

6. A composition according to claim 4 in aqueous alcohol solution.

7. A composition of matter comprising about 6 to 40 parts by weight of a surface active quaternary ammonium compound, about 5 to 40 parts by weight of a non-ionic surface active agent, and 1 to 4 parts by weight of chlorothymol.

8. A composition of matter comprising about 6 to 40 parts by weight of a surface active quaternary ammonium compound, about 5 to 40 parts by weight of a non-ionic surface active agent, about 1 to 4 parts by weight of chlorothymol, and 2 to 10 parts by weight of essential oils.

9. A composition according to claim 8 in aqueous alcohol solution.

10. A composition of matter possessing synergized anesthetic properties comprising an aqueous solution of a surface active quaternary ammonium compound, chlorothymol, and a non-ionic surface active agent selected from the group consisting of alkylaryl polyethylene glycols, alkylpolyoxyethylene alcohols, fatty acid amides, and amide ethers of fatty acids, said first constituent being present in said solution with regard to the latter constituent in weight proportions of between about 0.15 and 8.

11. A composition of matter according to claim 10 in aqueous alcohol solution.

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