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COMPOSITION FOR COUNTERACTING MICROORGANISMS

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This invention relates to compositions of matter for counteracting microorganisms, i. e., germs, including bacteria, fungi, and the like; and more especially to compositions in which some or all of the following properties are utilized: bactericidal, antiseptic, fungicidal, detoxifying, bacteriostatic, prophylactic and to novel chemical compounds having such properties. The invention relates particularly to such compositions which possess some or all of the aforementioned properties to a marked degree and which comprise one or more quaternary ammonium compounds.

In a prior patent, No. 2,295,504, dated September 8, 1942, I have disclosed that the acylated quaternary ammonium compounds, having an aliphatic group of 14 to 18 carbon atoms attached to the ammonium nitrogen atom, are particularly advantageous in compositions for counteracting microorganisms. Within that class the cetyl dimethyl carbethoxy methyl ammonium compounds were claimed as particularly advantageous. I have now found that analogous quaternary ammonium compounds of the acetox type have similar advantages and in some respects are surprisingly superior. Certain of these compounds are among the most advantageous for practical use in bactericidal, antiseptic, fungicidal, bacteriostatic, etc., compositions.

The object of my invention, therefore, was to make available novel compositions of matter which combine high efficacy as bactericidal, antiseptic, fungicidal, detoxifying, bacteriostatic and prophylactic agents against different types of pathogenic micro-organisms, and compatability in effective concentrations with human tissues and body fluids and those of other higher organisms as well, as with common ingredients of pharmaceutical compositions, and low cost of manufacture from readily available materials.

I have achieved this object by compositions the essential feature of which is the chemical combination represented by the formula:



wherein one of said R's represents an acylated aliphatic group containing an acetox group in which the —COO— group is connected to the nitrogen-atom-containing portion of the quaternary ammonium compound through the —O— atom of said —COO— group.

Another R represents a high molecular weight aliphatic group, advantageously cetyl, but which may be a saturated or unsaturated radical containing fourteen to eighteen carbon atoms in its essential chain, and may be a forked or a straight chain, and which may also contain substituents, for example, the hydroxyl, halogen, carbethoxy and amino groups, etc., which are such or so attached as to leave substantially the identity on the essential chain; and the remaining R's represent low molecular weight groups, advantageously hydrocarbon groups of not more than 4 carbon atoms, which may be separate or joined together to form a heterocyclic ring with the ammonium nitrogen atom.

X stands for any acid ion constituent, which forms soluble quaternary ammonium compounds of this type, for example, —Cl, —Br, —I, —NO₃, —SO₄, —OCOCH₃, —C₆H₅SO₃, —OH, —PO₄, —OCOC₆H₅, —CO₃, —OCOC₆H₄OH, the dicarboxylic and tricarboxylic acids, such as tartaric and citric, and lower fatty, etc., acids insofar as they form soluble salts of these quaternary ammonium compounds. Polyvalent acid radicals may combine several similar quaternary ammonium groups of the above type into a single molecule, or one such group may be combined with the acid while remaining valences of the acid radical are satisfied by different radical or cations or by hydrogen.

The acid ion constituent used in these compounds may also influence the properties, and especially solubility, toxicity, and surface activity. For bactericidal purposes, I have found that in general the bromides and chlorides are the best compounds in these respects.

The following compounds will illustrate my invention specifically:

Aliphatic quaternary ammonium salts

Chemical name	Critical killing dilution		Phenol coefficient		Approximate water solubility
	<i>E. typhi</i>	<i>Staph. aureus</i>	<i>E. typhi</i>	<i>Staph. aureus</i>	
β-Acetoxethyl cetyl dimethyl ammonium bromide.....	1:40,000	1:44,000	333	488	1:80 gels.
β-Acetoxethyl cetyl dimethyl ammonium iodide*	1:10,000	1:42,000	83	466	
β-Acetoxethyl cetyl dimethyl ammonium p-hydroxybenzoate*	1:8,000	1:24,000	66	268	1:30
β-Acetoxethyl cetyl dimethyl ammonium nitrate*	1:7,000	1:38,000	58	422	1:40
β-Acetoxethyl cetyl diethyl ammonium bromide.....	1:12,000	1:60,000	100	666	1:10
Cetyl di-n-butyl acetoxethyl ammonium bromide.....	1:16,000	1:52,000	133	577	-----

*Compounds marked with asterisk were not purified as well as the other compounds.

The above data represent the results of actual tests with the respective compounds of the highest purity available at the time. With the exception of the compounds marked with an asterisk, these are believed to be substantially pure—i. e. of a purity such as one would expect to use for pharmaceutical applications of my invention. However, as the degree of purity is not absolutely uniform among these several compounds tested, allowances must be made in comparing the respective values given. Increase in purity in cases where comparative tests have been made with the partially purified or commercial grade chemicals as against the corresponding highly purified compounds has produced significant increases in activity. Thus, for example, β -acetoxyethyl cetyl dimethyl ammonium bromide, made from chemicals as purchased commercially showed critical killing dilution of 1:12,000 against *E. typhi* and 1:36,000 against *Staphylococcus aureus* and when further purified and retested these were shown to be increased respectively to 1:40,000 and 1:44,000.

It will be noted that the compounds above listed have the cetyl group as their high molecular weight aliphatic hydrocarbon group, that is, the groups containing sixteen carbon atoms. These compounds have been found to be of especially high bactericidal efficacy on various types of pathogenic organisms, low toxicity to higher animals and humans, good surface tension depressing, penetrating and emulsifying power, are non-irritating in effective concentrations and have good detoxifying power.

For the three low molecular weight hydrocarbon groups of the formula hereinabove described it has been found, in practice, that the methyl, ethyl, butyl and acetoxyethyl groups are especially satisfactory.

The bromides, chlorides and the metho-sulfates are most active of the compounds tested; and, generally speaking, the nitrates and the iodides are suitable. In general, organic salts are not so good as the mineral acid salts, although the benzoates, salicylates, tartrates, and aromatic aliphatic acids such as the hydrocinnamates are quite good. The higher fatty acids give the poorest results especially in aqueous compositions and usually give relatively insoluble salts, and for this reason fatty acids and fatty acid soaps should be avoided in using compositions of my invention. Benzoates and salicylates which easily form gels have been found particularly suitable for lotions, etc. The compounds similar to the metho-sulfates having low molecular weight organic groups and a quaternary ammonium group of the type defined both combined with a polybasic acid, are found as a group to be very good, and relatively more highly effective against *E. typhi*.

It should be understood, of course, that although these conclusions are drawn from tests with numerous compounds which have been synthesized and tested for the purpose of determining trends toward better antiseptic, germicidal, etc., properties, still they should not be regarded as absolute, but are given rather as indications in order to assist others in choosing the best compounds and perhaps discovering better compounds within the scope of my invention. Like all conclusions in chemistry, these should be taken and used with caution, and it should be understood that my invention does not depend upon the correctness of these conclusions; and I do not wish to be bound thereby.

It will be understood, of course, that the fig-

ures given for activity against the two organisms named cannot be taken as absolute, since they will vary to some degree from test to test with variations in the cultures used; and I have found also that impurities present may have a substantial influence on the exact figure obtained by such a test, although it is an advantage of these compositions that they retain strong activity in the presence of substances which would normally occur during use.

As will be seen from the above figures, these compositions are among the most active thus far discovered, and at the same time they are among the best with respect to low toxicity to humans and animals and with respect to retention of activity in the presence of carbohydrates, especially sugars, proteins, serum or other substances with which such micro-organisms are commonly found in their active life.

The compounds of my invention are active in aqueous and oleaginous compositions and tinctures.

Another valuable quality of these compounds is their relative immunity to acidity and alkalinity. This quality and particularly the relative immunity to presence of iron, calcium and magnesium are especially important in mouth washes, tooth pastes, tooth powders, and antiseptic cleaning compositions for general use, in all of which an alkaline reaction may be important.

These qualities and immunities and the fact that the compounds are comparatively tasteless, odorless and non-staining, make it possible to use compositions including these quaternary ammonium compounds in compositions which contain flavoring, coloring, therapeutic or healing ingredients, and in various pharmaceutical, cosmetic and prophylactic compositions. The compositions of my invention may also be used as preservatives in all kinds of materials, including biological materials, fruits, vegetables and grains, etc., and in general wherever organic decomposition or putrefaction might occur. When used on fruits or vegetables it is found that their penetrating and emulsifying power assists in removal of spray residues as well as assuring destruction of decay infections.

Tests that have been made show that these compounds have a remarkable detoxifying action even in fairly dilute solutions.

In the concentration required for disinfection and purification processes they do not injure or stain the human skin and may, therefore, be used for disinfecting the skin, particularly the hands. Furthermore, it has been observed that these compounds in dilutions of 1 to 1,000 and less have a low surface tension for the most part in the range between 30-40 dynes/cm.², thus insuring good penetration.

The ammonium compounds of the present invention may be used in substance as well as in solution or emulsion and, if desired, in admixture with each other and/or with other active or inert substances such as powder, ointment bases, creams, etc.

These compounds have the further advantage that they show definite bactericidal action in oils. It has also been observed that these compounds are soluble to a certain extent in vegetable oils, such as olive or almond oils and that the presence of a small amount of benzyl alcohol greatly increases their solubility in oil. Hence these compounds will be of desirable use in rendering ointment bases bactericidal, for example the common petrolatum type of ointments. In addi-

tion to their use in the oil soluble ointment type, we also find that they have decided germicidal action in water soluble jellies, for example, in a tragacanth base.

It is not necessary that other ingredients should be used, but generally we find that a simple water solution or tincture will be most useful as a general antiseptic.

One very valuable composition, for example, is an aqueous solution diluted 1:1,000. This may be further diluted for use in cleansing or dressing wounds, for cleaning and sterilizing solutions, for use as a mouth wash, etc. For hospitals and other users who prefer more concentrated solutions, e. g., to save storage space, I may supply an aqueous solution in dilution of 1:250 or less.

For treating wounds and skin infections and for disinfecting instruments which are subject to rusting, a tincture is very useful, for example 1:1,000 in 30-40% ethyl alcohol.

Other illustrative compositions in which any of these quaternary ammonium germicides may be used are:

Mouth wash:

Germicide	per cent.	.02-.04
Boric acid	do	1
Alcohol	do	20-30
Flavor	As required	
Color	As required	
Water q. s.	per cent.	100

Skin antiseptic:

Germicide	per cent.	1-5
Dye	As required	
Alcohol	per cent.	40-50
Water q. s.	do	100

Cough drops:

Germicide	per cent.	.1
Aromatics	As required	
Sugar q. s.	per cent.	100

Lipstick:

Germicide	per cent.	.1
Beeswax	do	33
Lard	do	12
Castor oil	do	49
Perfume and color q. s.	As required	

Dentifrice (paste or powder):

Germicide	per cent.	.1
CaCO ₃	do	50
Tricalcium phosphate	do	25
Magnesium carbonate (or hydroxide)	do	24
Saccharin and flavor	do	.9
Wetting agent	do	.1

Nose drops:

Germicide	per cent.	.04-.02
Ephedrine SO ₄	do	1
Dextrose	do	4
Water q. s.	do	100

Germicidal ointment:

Germicide	per cent.	0.1
Hydrous lanolin	do	50.0
Petrolatum	do	50.0

Antiseptic medicated skin cream:

Germicide	per cent.	0.1
Glyceryl monostearate	do	10.0
Glycerin	do	5.0
Water	do	85.0

Lubricating jelly:

Germicide	per cent.	0.1
Tragacanth	do	1.0
Glycerin	do	15.0
Water q. s.	do	100

These, of course, are only examples; and it should be understood that their proportions can

be varied substantially and that numerous other types of compositions are within the scope of the invention.

In dentifrices and mouthwashes the sugar and acid immunity of the germicide are especially important qualities in view of the recent evidence that dental caries is due to growth of lactic acid bacillus. In oil base compositions, the emulsifying or surface tension reducing quality of these germicides is of utmost importance, because it breaks down the barrier of the interface and allows the germicide in the oil solution to become effective in the body fluids and/or the cell fluids of the organisms against which they are used.

These germicides also lend themselves well to germicidal hand cleaners of the type in which a wetting or lathering agent is absorbed on a carrier such as a colloidal clay, e. g., bentonite, diatomaceous earth, pumice, etc. (which may also act as an abrasive or scouring agent), and pressed into cakes with or without a binder adapted to delay disintegration in water. Such wetting agents, for example, as sulfonated aromatic ether alcohols (e. g., Triton Suds), sodium salt of alkyl naphthalene sulfate (Alkanol), aromatic sodium sulfonates (Ultra Wet), sodium oleyl amino ethyl sulfate (Igepon), may be used in this way combined with the germicides of my present invention to the extent of 1 to 10%, or a crude quaternary ammonium compound of the type above described may serve both as the detergent wetting agent and as antiseptic when mixed with a suitable carrier.

The compounds of my present invention also have the valuable property of forming remarkably stable dispersions of colloidal metals and insoluble salts. This has been found especially valuable in compositions which combine the valuable therapeutic properties of colloidal silver or colloidal silver salts with the remarkable germicidal properties of these quaternary ammonium compounds.

The compositions contemplated by the present invention are made conveniently by chemical methods known to those skilled in the art, for example, by reacting upon an aliphatic amine with a reactive halide of a higher molecular aliphatic hydrocarbon.

Alternatively, amines, which already contain a higher molecular aliphatic group, may be reached with aliphatic halide, sulfate, acetate, etc., to form the same type of ammonium salt. It has also been observed that the corresponding halides, sulfates, nitrates, salicylates, benzoates, acetates, tartrates, etc., can easily be prepared by a prolonged boiling of the bromide in an organic solvent with the corresponding salt of the alkali, alkaline earth or heavy metal. By the above reactions high molecular weight quaternary ammonium compounds are obtained, some of which are crystalline, some viscous liquids, and some wax-like substances, which, in general, depending upon the acid radicals, readily dissolve in water, forming stable, odorless, colorless and relatively non-toxic solutions.

Since, as stated above, the activity of these compounds is decreased by substituting aliphatic groups of higher or lower molecular weight, especially above 18 carbon atoms or below 14, it is desirable to purify either the final compounds or to use pure reagents in their manufacture. If substantial amounts of the higher or lower homologs are permitted in the final product, they will affect the antiseptic, etc., strength or activity of the product which, therefore, can be accurately

specified only after careful analysis and calculation or actual quantitative tests.

The following examples will serve to illustrate some methods of preparing products embodying the principles of this invention which are suitable for use in the illustrative compositions given above, without being restricted thereto:

Example No. 1

17 parts by weight of β -bromoethylacetate and 15 parts by weight of diethylamine are kept at 40° C. for two days, then diluted with an equal volume of ether and the precipitate of diethylamine hydrobromide filtered. The filtrate was distilled to give 15 parts of β -diethylaminoethylacetate, B. P. 80–86° at 28 mm. or 70–77° at 18 mm., N_D^{20} 1H27, d_4^{20} 0.976. This compound and its preparation are described in the literature.

A mixture of 11 parts of the β -diethylaminoethyl acetate and 20 parts of cetyl bromide was heated at 70–75° for 3 to 4 weeks. The resulting mixture was then crystallized from a mixture of acetone and ether, then from acetone. The crystalline product obtained was β -acetoxyethyl cetyl diethylammonium bromide, containing a small amount of β -diethylaminoethyl acetate hydrobromide and melted at 69–72°.

Example No. 2

A mixture of 13.5 parts of pure cetyl dimethylamine and 8.4 parts of β -bromoethyl acetate is heated at 70° C. for 24 hours, then crystallized from 75–100 parts of acetone, washed with ether, and dried to give a crystalline product consisting essentially of β -acetoxyethyl cetyl dimethyl ammonium bromide, M. P. 83–85° C. and dissolving readily in five parts of water.

What is claimed is:

1. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a cetyl beta-acetoxy-ethyl dimethyl ammonium salt.

2. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a cetyl beta-acetoxy-ethyl dimethyl ammonium bromide.

3. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a cetyl beta-acetoxy-ethyl diethyl ammonium salt.

4. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a cetyl beta-acetoxy-ethyl diethyl ammonium bromide.

5. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a cetyl beta-acetoxy-ethyl di-N-butyl ammonium salt.

6. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a cetyl beta-acetoxy-ethyl di-N-butyl ammonium bromide.

7. A germ counteracting composition which comprises as the essential germ counteracting ingredient therein a quaternary ammonium compound having attached to the quaternary nitrogen atom one cetyl group, one acetoxy group, two hydrocarbon radicals of less than five carbon atoms, each, and an anion which forms soluble quaternary ammonium compounds.

8. A germ counteracting composition which comprises, as the essential germ counteracting ingredient therein, a soluble quaternary ammonium compound, the ammonium nitrogen of which has attached thereto, besides an anion which forms a soluble quaternary ammonium compound, one higher aliphatic radical of not less than 14 nor more than 18 carbon atoms, and one acylated lower molecular weight aliphatic radical including an acetoxy group, the carboxyl of which is connected through its —O— atom to the ammonium-nitrogen-containing portion of the molecule, and has attached thereto by two of its remaining valence linkages at least one lower molecular weight hydrocarbon radical, the sum of the carbon atoms in the portion of the molecule thus attached through said two valence linkages being less than 8.

9. A germ counteracting composition which comprises an oleaginous vehicle and, as the essential germ counteracting ingredient therein, a soluble quaternary ammonium compound, the ammonium nitrogen of which has attached thereto, besides an anion which forms an oil-soluble quaternary ammonium compound, one higher aliphatic radical of not less than 14 nor more than 18 carbon atoms, and one acylated lower molecular weight aliphatic radical including an acetoxy group, the carboxyl of which is connected through its —O— atom to the ammonium-nitrogen-containing portion of the molecule, and has attached thereto by two of its remaining valence linkages at least one lower molecular weight hydrocarbon radical, the sum of the carbon atoms in the portion of the molecule thus attached through said two valence linkages being less than 8.

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