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COMPOSITION OF MATTER

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This invention relates to compositions of matter for controlling micro-organisms, including bacteria, fungi, and the like, and/or mitigating their effects; and more especially to compositions in which some or all of the following properties are utilized: bactericidal, antiseptic, fungicidal, 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.

Prior to my invention it has been suggested to use certain amines and quaternary ammonium compounds for bactericidal, fungicidal and general disinfecting purposes; and it has also been suggested that, when quaternary ammonium compounds contain, attached to the nitrogen, besides other organic radicals, at least one high molecular weight aliphatic hydrocarbon radical, such compounds may display bactericidal and fungicidal properties. Quaternary ammonium compounds possessing such bactericidal and fungicidal properties have been tested only to a limited extent.

The present invention aims to provide compositions of matter belonging to the general class of quaternary ammonium compounds which will be more efficacious as bactericidal, antiseptic, fungicidal and bacteriostatic agents than those heretofore available and which are, in general, safer than antiseptics heretofore in general use.

I have found by extensive experiments and tests with compositions containing quaternary ammonium compounds that compositions containing a cetyl trimethyl ammonium salt or hydroxide or similar compositions are most surprisingly efficacious for the purposes of this invention, as expressed above, being at the same time extremely effective against the undesirable micro-organism, having very low and practically negligible toxicity in effective concentrations and having a penetrating power which is often of great practical importance in compositions of my invention.

The positive ion constituent used in the cetyl trimethyl ammonium compound may be any which forms a soluble compound and which does not itself have objectionable properties either alone or by interaction with other ingredients of the composition in which the ammonium compound is used. Among those which may be used satisfactorily are, for example: —OH, —Cl, —Br, —I, $—NO_3$, $=SO_4$, $=CO_3$, $\equiv PO_4$, $—OCOCH_3$, $—OCOC_6H_5$, $—OCOC_6H_4OH$, metho-sulfate, etho-sulfate and similar ions, the dicarboxylic and tricarboxylic acids such as citric and tartaric, and the lower fatty acids; polyvalent acid radicals may combine several similar quaternary ammonium groups of the above specified type into a single molecule or one such group may be combined with the acid while the remaining valences of the acid ion are satisfied by hydrogen or a different cation or group, especially by a low molecular weight organic group, as in the metho-sulfates. Anions which forms insoluble ammonium compounds, particularly the higher fatty acids such as are used in ordinary soaps are not recommended either as the original anion of the ammonium compound or in any ionized ingredient of the same composition.

Among the compounds which have been found to be useful for purposes of my invention are the following:

Aliphatic quaternary ammonium salts

Chemical name	Critical killing dilution		Phenol coefficient		Approximate water solubility
	E. typhi	*Staph. aureus*	*E. typhi*	*Staph. aureus*	
Cetyl trimethyl ammonium acetate	1:13,000	1:38,000	108	488	1:8
Cetyl trimethyl ammonium benzoate	1:28,000	1:56,000	233	622	1:8
Cetyl trimethyl ammonium bromide	1:38,000	1:88,000	316	977	1:25
Cetyl trimethyl ammonium chloride	1:31,000	1:55,000	258	555	1:2,000
Cetyl trimethyl ammonium cyanide	1:40,000	1:44,000	333	488	
Cetyl trimethyl ammonium hydroxide	1:64,000	1:48,000	533	533	
Cetyl trimethyl ammonium iodide	1:28,000	1:70,000	233	777	
Cetyl trimethyl ammonium hydrocinnamate	1:40,000	1:60,000	333	666	1:10
Cetyl trimethyl ammonium laurate	1: 8,000	1:32,000	66	355	1:250
Cetyl trimethyl ammonium nitrate	1:57,000	1:55,000	450	633	
Cetyl trimethyl ammonium ricinoleate		1: 2,000		22	
Cetyl trimethyl ammonium salicylate	1:22,000	1:48,000	182	533	1:6
Cetyl trimethyl ammonium sulfate	1:34,000	1:44,000	283	488	1:100
Cetyl trimethyl ammonium tartrate	1:32,000	1:44,000	266	488	
Cetyl trimethyl ammonium metho-sulfate	1:56,000	1:80,000	435	888	
Cetyl trimethyl ammonium ortho phosphate	1:20,000	1:32,000	166	355	

All the compounds given in the above list were prepared from a high purity commercial cetyl alcohol which actually contained small amounts of stearyl and myristyl alcohols as well. Parallel tests with a number of these compounds carefully purified to eliminate the stearyl and myristyl compounds have shown in every case much higher killing dilutions. Moreover, as these impurities are not absolutely uniform, some allowance needs to be made in comparing values for different compounds.

The killing dilutions are for solutions in a menstruum of 50% alcohol, 40% water, 10% acetone. The "Phenol coefficient" is a convenient index obtained by dividing the critical killing dilution by the critical killing dilution of phenol for the same organism.

It should be understood that these are only examples given as indications in order to assist others in choosing the best compounds and perhaps discovering better compounds within the scope of my invention.

It will be understood, of course, that the figures 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. Using *Staphylococcus aureus* and *Bacillus typhosus* as the test organisms it was found, for example, that slightly impure cetyl trimethyl ammonium bromide with 10% by volume of sterile serum added to the diluted germicide completely killed the test organisms in 10 minutes in the following dilutions:

	Staph. aureus		*B. typhosus*	
	No serum	Serum	No serum	Serum
Alcoholic	1:84,000	1:12,000	1:36,000	1:5,000
Aqueous (neutral)	1:80,000	1:7,500	1:18,000	1:6,000
Aqueous (pH 2.0)	1:21,000	1:4,500	1:55,000	1:6,000
Aqueous (pH 10.5)	1:47,000	1:6,000	1:24,000	1:7,000

This test also illustrates another valuable quality—the relative immunity of these compositions to acidity and alkalinity. This quality and particularly the relative immunity to presence of calcium and magnesium are especially important in tooth pastes, tooth powders, and antiseptic cleaning compositions for general use, in all of which an alkaline reaction may be important.

These qualities make it possible to use compositions including these quaternary ammonium compounds in compositions which contain flavoring, coloring, therapeutic or healing ingredients; and the compositions of my invention may also be used as preservatives in all kinds of materials, including fruits and vegetables, grains, etc., wood, clothing, adhesives, biological materials, 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.

In their use as general antiseptics their immunity to acids and alkalies is very important, and also their immunity to iron salts, calcium salts, and others which may be encountered in normal disinfecting uses.

Tests that have been made, especially with cetyl trimethyl ammonium bromide, show that these compounds have a remarkable detoxifying action even in fairly dilute solutions. It was observed, for example, that when 0.25 cc. of a 1:1,000 cetyl trimethyl ammonium bromide was added to 0.3 cc. of a standardized 1:1,000 tetanus toxin and injected subcutaneously into 325–350 gm. guinea pigs, that the animals showed no appearances of paralysis or death after 5 days observation, while the control guinea pigs when injected with 0.3 cc. of the 1:1,000 standardized tetanus toxin under the same conditions all died within 70 hours. This shows that the above described compounds have unusual detoxifying action in extremely dilute solutions, so that they may at the same time be used to kill or control infection and to counteract poisons resulting from the infection. This test may be compared with other detoxifying compounds such as formaldehyde, halogen and hydroxy compounds of salicyclic acid and other derivatives which show comparable detoxifying action only in high concentrations, e. g., in the neighborhood of ¼ per cent.

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 when used as skin antiseptics.

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 vegetable 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, for example, cetyl trimethyl ammonium bromide is soluble 1:100 in a solution containing benzyl alcohol, almond oil and petrolatum. Hence these compounds will be of desirable use in rendering ointment bases bactericidal, for example the common petrolatum type of ointments. In addition to their use in the oil soluble ointment type, we also find that they have decided germicidal action in water soluble jellies, for example, cetyl trimethyl ammonium bromide 1:5,000 in a tragacanth base gives definite germicidal action to this type of jelly.

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 of cetyl trimethyl ammonium bromide 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 cetyl trimethyl ammonium salicylate in dilution of 1:250 or less. This latter solution is a viscous liquid and in lower dilutions approaches even a jelly condition, but for actual use these will ordinarily be diluted, e. g., with from 10–100 times its weight of water, so that the final solution is entirely watery.

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

A composition very useful for mouthwash and similar purposes is a solution of cetyl trimethyl ammonium salicylate 1:10,000 in 18–20% ethyl alcohol with aromatic oils added for flavoring.

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

MOUTH WASH

	Per cent
Germicide	.02–.04
Boric acid	1
Alcohol	20–30
Flavor	As required
Color	As required
Water q. s	100

SKIN ANTISEPTIC

Germicide	.1–.5
Dye	As required
Alcohol	40–50
Water q. s	100

COUGH DROPS

Germicide	.1
Aromatics	As required
Sugar q. s	100

LIPSTICK

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

DENTIFRICE

(Paste or powder)

Germicide	.1
$CaCO_3$	50
Tricalcium phosphate	25
Magnesium carbonate (or hydroxide)	24
Saccharin and flavor	.9
Wetting agent	.1

NOSE DROPS

Germicide	.04–.02
Ephedrine SO_4	1
Dextrose	4
Water q. s	100

GERMICIDAL OINTMENT

Germicide	0.1
Hydrous lanolin	50.0
Petrolatum	50.0

ANTISEPTIC MEDICATED SKIN CREAM

Germicide	0.1
Glyceryl monostearate	10.0
Glycerin	5.0
Water	85.0

LUBRICATING JELLY

Germicide	0.1
Tragacanth	1.0
Glycerin	15.0
Water q. s	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 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. The commonly known wetting agents 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 tri-methyl amine with a reactive cetyl halide.

Alternatively, cetyl dimethyl amine may be reacted with methyl 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, metho-sulfates, 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 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 without being restricted thereto:

Example No. 1

The reaction is effected between approximately equimolar parts by weight of trimethylamine (33% solution in MeOH) (a slight excess often is advisable) and cetyl bromide at room temperature. After cooling, the crystalline material is filtered off and recrystallized from ethyl acetate. The cetyl-trimethyl ammonium bromide thus obtained forms colorless plates, melting at 235°–237° C. and is readily soluble in water.

Example No. 2

Equimolar parts by weight of trimethylamine (35% solution in methyl alcohol) and cetyl chloride are heated together in a pressure flask at 100° C. The mixture is worked up as in Example No. 1. The resulting cetyl-trimethyl ammonium chloride is a white crystalline solid, very soluble in water,

Example No. 3

Equimolar parts of silver sulfate and cetyl trimethyl ammonium bromide are heated for ten hours in boiling alcohol. The resulting cetyl trimethyl ammonium sulfate may be separated from the silver bromide by filtration. Other salts may be formed from the halides in a similar way, e. g., salicylate, tartrate, benzoate, nitrate, metho-sulfate, etc.

Example No. 4

One mol of cetyl trimethyl ammonium bromide dissolved in alcohol is refluxed with 1 mol of silver nitrate for four hours, then allowed to cool. The silver bromide is filtered off and the alcoholic solution concentrated and precipitated with ether. The cetyl trimethyl ammonium nitrate is filtered off and recrystallized from ethyl acetate. In a similar manner the cetyl trimethyl ammonium sulfate, metho-sulfate, benzoate, salicylate, tartrate, and acetate are prepared by refluxing in alcohol, molar proportions of cetyl trimethyl ammonium bromide and the sodium or silver salt of the corresponding organic acid.

Example No. 5

One mol of cetyl dimethylamine is allowed to react at about 60° C. with 1 mol of dimethyl sulfate. The cetyl tri-methyl ammonium metho-sulfate formed is separated and recrystallized as in the other examples.

Example No. 6

Equimolar proportions of cetyl trimethyl ammonium chloride and dimethyl sulfate are heated for about 24 hours at 125° C. with distillation of the methyl chloride formed. The cetyl trimethyl ammonium metho sulfate formed is separated and recrystallized from ethyl alcohol or ethyl acetate. This same method may be used also for other alkyl-polybasic acid salts of the ammonium compounds and other salts than the chloride, e. g., other halides, nitrates, etc., may be used provided only that the temperature of heating is chosen so that the ammonium salt and the alkyl salt used are not very volatile, whereas, the alkyl salt formed is sufficiently volatile so that it is readily distilled off from the reacting mixture.

The word "inhibiting" as used in the following claims is intended to include the killing of micro-organisms as well as rendering them inactive or harmless, e. g. as in bacteriostatic action.

This application is a continuation in part of my prior copending application Serial No. 222,448, filed August 1, 1938.

What I claim is:

1. A micro-organism inhibiting composition which comprises as the essential active ingredient, a soluble cetyl trimethyl ammonium compound.

2. A micro-organism inhibiting composition which comprises as the essential active ingredient, cetyl trimethyl ammonium bromide.

3. A micro-organism inhibiting composition which comprises as the essential active ingredient, cetyl trimethyl ammonium nitrate.

4. A micro-organism inhibiting composition which comprises as the essential active ingredient, cetyl trimethyl ammonium metho-sulfate.

5. A micro-organism inhibiting composition which comprises as the essential active ingredient, a salt of a polybasic acid with a low molecular weight organic group and a cetyl tri-methyl ammonium group.

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