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2,828,316

QUATERNARY COMPOUND OF BENZETHONIUM CHLORIDE AND SACCHARIN

August J. Pacini, Tarrytown, Lester E. Amster, New York, and Richard A. Duff, Levittown, N. Y.

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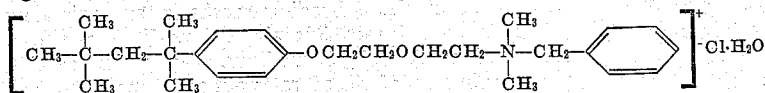
1 Claim. (Cl. 260—301)

The present invention relates to pharmaceutical compositions, and especially to a composition which is a product, or mixture, of a quaternary compound and saccharin.

In the past, there has been an ever expanding group of cationic quaternary compounds which have been made available as powerful germicides. These germicides are referred to under a variety of designations, viz., cationic germicides, quaternary ammonium compounds, surface active sterilizing agents and by certain groups, as quaternary detergents. These compounds are all available through regular commercial channels under a variety of trade names. It can be readily appreciated that a wide variety of cationic germicides will eventually be made available as the possibility of variation in chemical structure with the quaternary ammonium central characteristic offers a wide scope of compounds.

In accordance with the present invention, we have found, contrary to the teaching of prior art, that non-bitter and highly effective bacteriostatic and bactericidal compounds may be prepared as a reaction product, or mixture of quaternary ammonium compounds with saccharin.

Thus it is seen that quaternary ammonium compounds are characterized by their ability to exert powerful bacteriostatic and/or bactericidal effectiveness in dilutions that are completely non-toxic to the human organism, by an ability to reduce surface tension thereby exerting more than ordinary surfactant penetration, and by the further property of exercising pronounced deodorant capacity. Such quaternaries, however, are intensely bitter to the taste causing them to be rejected for local and/or systemic effectiveness where indications exist for the use of their other properties. Typically illustrative of a useful quaternary for this purpose is benzethonium chloride U. S. P. XV, represented by the following chemical configuration:



Benzethonium chloride solution is recognized in U. S. P. XV as a local anti-bacterial suitable for topical application as a 1:1000 solution to the skin, or a 1:5000 solution to the eye or nose. It is clear, colorless, odorless but intensely bitter. Sprayed into the throat in concentrations of 1:100,000, aqueous solutions of benzethonium chloride U. S. P. exercise valuable therapeutic aid, particularly with respect to the control of inflammations that represent beginning surface infections. Benzethonium chloride is also known as Phemerol Chloride, Phemeride, and Hyamine, and is described in the Merck Index, 6th edition, page 735. Preparation of this compound is described in U. S. Patents No. 2,115,250, 2,170,111, and 2,229,024.

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Because of the lowered surface tension of benzethonium chloride solutions, they are enabled better to penetrate inaccessible folds, crypts, follicles and other bacterial hideaways present everywhere in the mucous surfaces of the fauces. Such easier access to nests of bacteria that may ordinarily escape viscous and non-surfactant solutions respond to the bacteriostatic and/or bactericidal properties of surfactant quaternary, thereby yielding improved hygienic advantages of many sorts including the control and even the prevention of local and/or systemic infections commonly known to develop at and from this portal of entry. Such organisms embedded in the mucous membranes of the fauces can escape attack by aqueous and even alcoholic mouthwashes despite their content of ordinary antiseptic ingredients when these are unable to reach other than the most superficially disposed germs. This is true also of quaternary compounds and other antiseptic substances that are made into sugared confections since the ratio of sugar to antiseptic material is such that in the dissolution of the lozenge, troche, pastille, "cough drop" or other, a thick viscous syrup is at first formed serving as a barrier by osmotic hindrance to the easy accessibility of the antiseptic to the depths required for effective reactivity. Such "candies" are useful as demulcents, but can be shown to exert only the barest and practically always a nil bactericidal value as contrasted with the same ratio of quaternary in an aqueous solution or in a sugar-free tablet or equivalent.

Many quaternaries, benzethonium chloride included, show a wide range of "incompatibility." For example, on page 25, of "Surface-Active Quaternary Ammonium Germicides," by Carl A. Lawrence, Academic Press Inc., New York, 1950, among other substances incompatible with alkyl dimethylbenzylammonium chloride, mention is made of saccharin. Such incompatibility is surmised when in the mixture of an aqueous quaternary solution produced for pharmaceutical compounding with other ingredients, a physical change appears in which a precipitate results. It is important to realize also that occasional physical admixtures may be made without the separation of a precipitate, but attended, nevertheless, with loss and even extinction of all bactericidal and/or bacteriostatic capacity.

When benzethonium chloride U. S. P. is mixed in molar equivalents with sodium saccharin U. S. P. in solution, and the mixture boiled, the following changes in physical appearance are observed: An oily liquid showing a specific gravity of approximately 1.14 separates as a layer

either above or below a clear layer solution. The position of the oily layer is regulated entirely by the solute concentration of the aqueous layer so that when this is great (above 1.14) the oily layer floats, and when it is small (below 1.14) the oily layer sinks.

Separation of the layers and subsequent evaporation to dryness of the aqueous phase (non-oily layer) yields a crystalline solid with characteristics that distinguish it from either sodium saccharin or benzethonium chloride.

This solid is bacteriostatic and/or bactericidal. It depresses surface tension such that an 0.1% solution of the solid gives approximately 36 dynes per square centimeter. It is not bitter, but somewhat sweet like the saccharin from which it is derived without, however, developing

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a bitter after-taste such as many individuals frequently experience in the case of saccharin. It has a melting point in excess of either sodium saccharin (226° C. to 230° C.) or benzethonium chloride (between 160° C. and 165° C.), and somewhere between 280° C. to 285° C. On chemical analysis, it yields very close to the following composition:

	Percent
Carbon -----	62.0
Oxygen -----	12.2
Nitrogen -----	4.3
Hydrogen -----	7.3
Sulfur -----	4.9
Chlorine -----	5.4
Sodium -----	3.5

From this compound, it is possible to separate sodium chloride. The composition suggests that some measure of interaction has resulted between benzethonium chloride and sodium saccharin yielding, in essence, benzethonium saccharin and sodium chloride. Such a reaction would be represented by the equation previously indicated.

Whether or not this precise chemical interaction takes place is still a matter of intensive investigation, the result of which is inconsequential with respect to the more important finding that the mixture or compound so produced exhibits the following properties:

- (1) It is bacteriostatic and/or bactericidal to an extent within the range that will be indicated subsequently.
- (2) It lowers the surface tension of water so that 0.1% solution in water gives a value of 36 dynes per square centimeter.
- (3) It retains some of the deodorant properties of the original benzethonium chloride from which it is derived.
- (4) It retains the sweetness, but not the after-bitterness, of the sodium saccharin from which it is derived.
- (5) It is completely devoid of the intense bitter taste of the original benzethonium chloride when used in equivalent concentrations based on equivalent bactericidal effect.
- (6) The substance is soluble in water and it is not precipitated therefrom by many of the substances that precipitate benzethonium chloride.

It is obvious that the compound and/or mixture retains the desirable therapeutic virtues of the benzethonium chloride from which it is derived and eliminates the bitterness that has precluded the use of benzethonium chloride in forms where it can exert its greatest therapeutic effectiveness.

The production of this compound and/or mixture, is illustrated in the following exemplary procedure:

Example 1.—150 grams of benzethonium chloride are dissolved in 400 to 600 cubic centimeters of water. 375 grams of saccharin sodium are dissolved in 400 to 600 cubic centimeters of water. These are not in the proportion of the molecular weight of each ingredient, the molecular weight of benzethonium chloride being 466.11 and that of sodium saccharin being 241.21. Both solutions are mixed and brought to a boil, the boiling maintained for one hour. In the course of boiling, a turbidity develops due to the dispersion of a water insoluble "oily" layer. After boiling, and on standing, the yellowish oily layer separates out at the bottom of the mixture. This layer seemingly retains some water and may measure from 8 to 10 ounces in volume. Overlaying the "oily" layer is a clear supernatant fluid. The clear fluid is removed from the "oily" layer, filtered and evaporated to dryness over a water bath. A recovery of from 250 to 290 grams of a white crystalline solid is obtained, the weight depending in part on the completeness with which the water layer is separated from the "oily" layer, and in part on the thoroughness with which the water bath drying is effected.

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The solid compound has a melting point above 280° C., is soluble in water, alcohol and acetone, is slightly sweet with no residue of bitterness and is bactericidal and/or bacteriostatic. For instance, a 1:25,000 concentration in water shows a phenol coefficient of approximately 1:1,500,000. An 0.1% solution of the solid shows a surface tension of 56 dynes per square centimeter. Administered in doses of 10 milligrams daily to a human subject over a period of four months, no evidence whatever of acute and/or toxic distress is observed. In lower animals, the LD-50 is greater than that usually stated for benzethonium chloride, being of the order of 750 instead of 500 for mice, and 900 instead of 765 for rats. An aqueous solution of the solid in water shows a pH of approximately 7.2 as distinguished from a pH of 7.0 for a similar solution of equivalent concentration of benzethonium chloride. The approximate analysis is about as follows:

	Percent
Carbon -----	62.0
Oxygen -----	12.2
Nitrogen -----	4.3
Hydrogen -----	7.3
Sulfur -----	4.9
Chlorine -----	5.4
Sodium -----	3.5

Since sodium chloride is present in the recovered material, and the percent of sodium and chlorine found are in stoichiometric proportion, such as appear in sodium chloride, and because the remaining composition answers to a stoichiometric combination of benzethonium and benzodulfimide, it is hypothesized that the product in question can be benzethonium benzosulfimide. If this hypothecon is correct, the resultant would represent, in part, the chemical reaction given previously.

Whether the hypothesis is true or false is not immediately consequential to the finding that the compound desired is achieved in the manner described and presents the properties outlined above, a surfactant, water soluble, odorless, slightly sweet and completely nonbitter, deodorant possessing approximately the same order of bacteriostatic and/or bactericidal effect as that of the original benzethonium chloride and greater than that of the sodium saccharin from which it was derived.

It is not necessary that the proportions indicated in Example 1 be followed meticulously in order to obtain the product. The same effect is obtained if other proportions are employed, the difference being in the yield and in the degree of sweetness presumably owing to more or less presence of unaltered sodium saccharin. For example:

Example 2.—A gram molecular equivalent of benzethonium chloride, approximately 466 grams, and a gram molecular equivalent of sodium saccharin, approximately 241 grams, are dissolved in about three liters of water. The solution is boiled for one hour. Approximately 530 cubic centimeters of oil separates out and some 330 grams of utilizable compound are derived by evaporating the water phase.

Example 3.—150 grams of benzethonium chloride are dissolved in 400 to 600 cubic centimeters of water. 375 grams of saccharin are suspended in 400 to 600 cubic centimeters of water. The solution and suspension are mixed and heated to boiling. After about an hour of boiling, a semi-solid residue will separate leaving a highly acid supernatant layer. The pH of this layer is about 1.5. Sufficient sodium hydroxide is now added completely to neutralize the solution and boiling resumed. The crystalline portion of the solids dissolves and a clear yellowish oily layer separates. From 250 to 300 grams of debittered quaternary active solid is recovered from the filtered and evaporated water layer. The formation of acid in this synthesis illustrates the ionic split of the

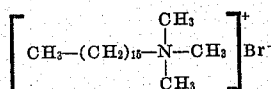
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benzethonium and saccharin, the cationic hydrogen of the saccharin combining with the anionic chlorine of the benzethonium to form hydrochloric acid, just as in Example 1, the cationic Sodium of the sodium saccharin combines with the anionic chlorine of the benzethonium chloride to produce sodium chloride.

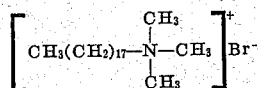
Quaternary ammoniums which are suitable for the practice of our invention and which are representative of the group are as follows:

Compound

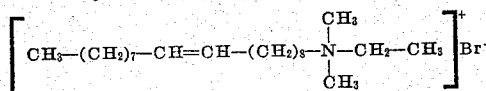
C. T. A. B., Cetavlon: Cetyltrimethylammonium bromide



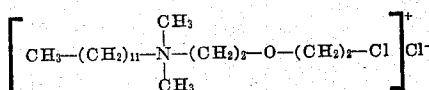
Product QB: Stearyltrimethylammonium bromide



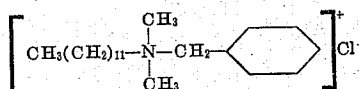
Onyoxide: Oleyldimethylethlammonium bromide



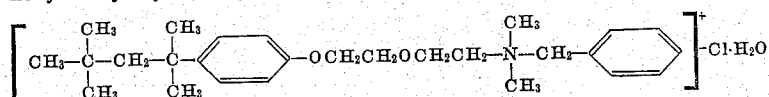
Isothan OX: Lauryldimethylchloroethoxylammonium chloride



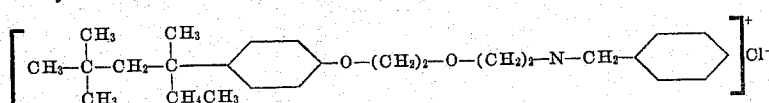
Nopoc QCL: Lauryldimethylbenzylammonium chloride



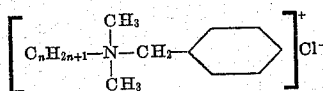
Hyamine 1622, Polymine D, Phemerol: Diisobutylphenoxyethoxyethyltrimethylbenzylammonium chloride



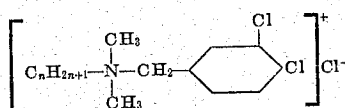
Hyamine 10X: Diisobutylcresoxyethoxyethyltrimethylbenzylammonium chloride



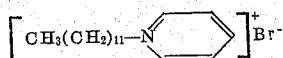
B. T. C., Roccal, Zephiran: Alkyl (C_8H_{17} to $\text{C}_{18}\text{H}_{37}$) dimethyl 3,4-dichlorobenzylammonium chlorides



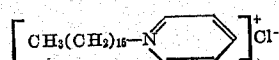
Tetrosan: Alkyl (C_8H_{17} to $\text{C}_{18}\text{H}_{37}$) dimethyl 3,4-dichlorobenzylammonium chlorides



Isothan Q4: Laurylpyridinium bromide

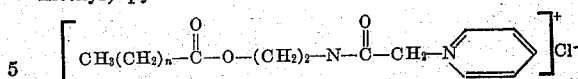


Ceepryn: Cetylpyridinium chloride

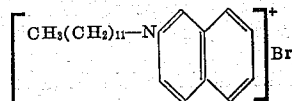


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Emulsept: N (higher acyl esters of colamino formylmethyl) pyridinium chloride



Isothan Q15: Laurylisoquinolinium bromide



In testing compounds of our invention, the following cultures may be used as test organisms: (1) *Escherichia coli*, a heat resistant strain from the National Institutes of Health; (2) *Aerobacter aerogenes* from the American Type Culture Collection; (3) *Aerobacter aerogenes*, a capsulated (slimy) strain found in paper mills; (4) *Micrococcus aureus*, isolated from drainage in wounds; (5) *Streptococcus cremoris*, from cheese starter organisms; (6) *Bacillus subtilis*, from American Type Culture Collection; (7) M-23, mesophilic flat sour strain isolated from beets, by the laboratory of the National Canners' Association; (8) No. 1518, facultative thermophilic flat sour strain isolated from peas, by the laboratories of the National Canners' Association; (9) No. 1503, obligate thermophilic flat sour strain isolated from corn, by the laboratories of the National Canners' Association.

The non-spore-bearing cultures are grown in 9 cc. of broth (tryptone 5 g., glucose 1 g., bacto-beef extract 3 g., distilled water 1 liter). Only 24 hour subcultures of 24 hour cultures are used in germicide tests, and at least three successive transfers (at least 24 hour intervals) are made prior to each test.

The spore-forming types are grown on slants (medium similar to above containing additional 15 g. Bacto agar) in 6 oz. flat bottles. The slants are inoculated by washing the surface with a 24-hour culture and incubated for one week. The bottles containing the cultures are then held at 35° F. until used. To prepare a culture for the

germicide tests, 120 cc. of a tryptone, glucose-beef extract broth are added to the slant and the bottle shaken

to suspend all growth. Nine cubic centimeter amounts of the suspended culture are transferred to sterile tubes and boiled for six minutes and quickly chilled.

The cultures of both spore-forming and non-spore-forming organisms are suspended in 9 cc. amounts of broth for the germicide test. By plate counts and comparable nephelometer observations the broth suspensions are standardized to approximately 500,000,000 organisms per cc.

The routine test procedure includes the use of 1 cc. of germicide solution of 10 times the desired final concentration added to the culture suspension and shaken. This method of adding a smaller amount of germicide to a larger amount of culture is preferred to the phenol coefficient method of the Food and Drug Administration in which a smaller amount of culture is added to a larger volume of germicide. It should be noted that this procedure constitutes a more severe test of the germicidal ability than the corollary of adding small amounts of cultures to large amounts of germicide as followed in the phenol coefficient procedure. Results by this method appeared to show fewer discrepancies ("skips") and are more capable of reproduction than results obtained by

the Food and Drug Administration Method for phenol coefficient.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is to be understood that variations and modifications may be made therein in accordance with the principles disclosed, without departing from the scope of the invention, which is to be limited solely by the appended claim.

I claim:

A bacteriostatic and bactericidal composition compris-

ing the water soluble reaction product of benzyldimethyl{2 - (p - 1,1,3,3 - tetramethylbutyl-phenoxy)ethoxy}-ethyl}-ammonium chloride and saccharin.

References Cited in the file of this patent

UNITED STATES PATENTS

2,725,326 Shibe et al. Nov. 29, 1955