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H. H. RELLER ET AL
ANTIBACTERIAL COMPOSITIONS

3,084,097

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FIG. 1.

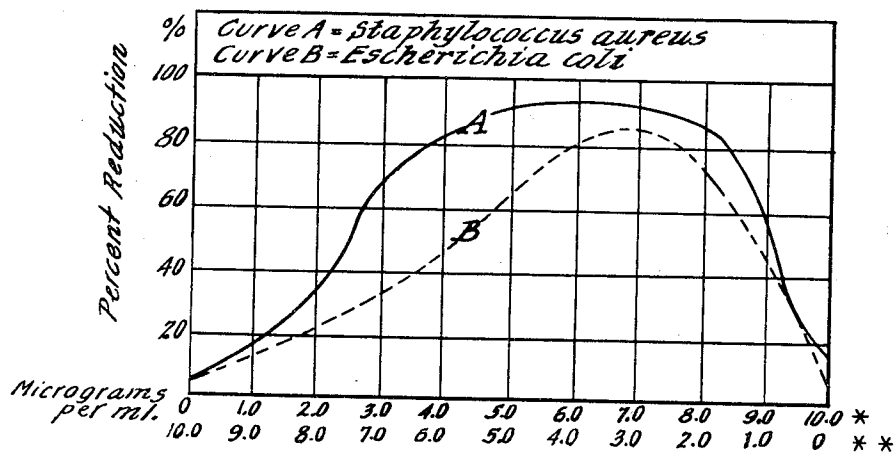
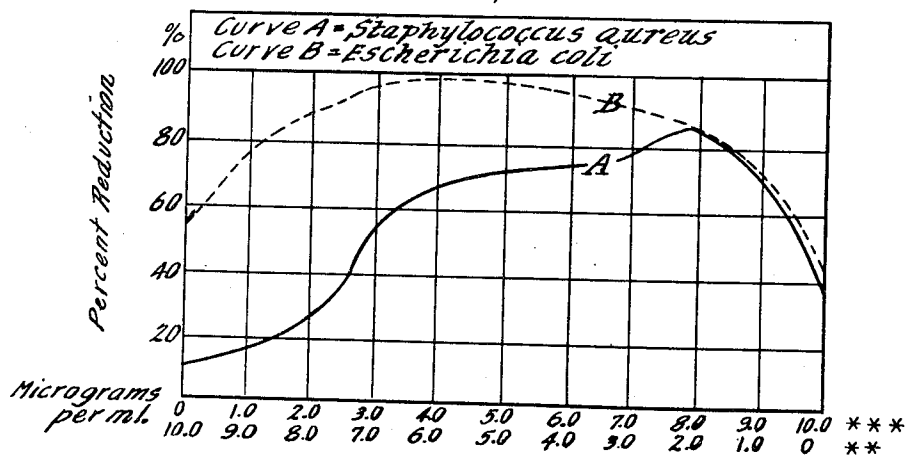


FIG. 2.



* Bis(3,5-dichloro-2-hydroxyphenyl) sulfide
** 3-trifluoromethyl-4,4'-dichlorocarbonyl
*** Bis(3,5,6-trichloro-2-hydroxyphenyl) methane

INVENTORS

Herbert H. Reller
William E. Jordan

BY

Richard C. Witte

ATTORNEYS

1

3,084,097

ANTIBACTERIAL COMPOSITIONS

Herbert H. Reller and William E. Jordan, Cincinnati, Ohio, assignors to The Procter & Gamble Company, Cincinnati, Ohio, a corporation of Ohio

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10 Claims. (Cl. 167—30)

This invention relates to improved anti-bacterial agents. More particularly, it relates to anti-bacterial agents which comprise in combination a halogenated bisphenolic compound and halogenated trifluoromethyl diphenyl urea.

The application of halogenated bisphenolic compounds as anti-bacterial agents is well known. For example, they have been successfully employed as anti-bacterial agents in detergent compositions, such as deodorant toilet bars, oral hygienic preparations, including toothpaste and mouthwash, and in various cosmetic formulations.

Anti-bacterial agents which have heretofore been employed in detergent compositions, including the said halogenated bisphenols, display certain inherent deficiencies which detract from their efficacy for such applications.

Gram-negative organisms are common contaminants of the skin and other surfaces upon which anti-bacterial detergent usage has been found desirable and it is therefore essential to reduce the population of these organisms as well as gram-positive organisms to attain the maximum beneficial effect. In general, anti-bacterial agents which have been found satisfactory for use in detergent milieu otherwise, display only slight activity against gram-negative organisms.

An additional disadvantageous characteristic peculiar to the bisphenolic compounds is photosensitivity. When bis(3,5,6-trichloro-2-hydroxyphenyl) methane and bis(3,5-dichloro-2-hydroxyphenyl) sulfide for example, are incorporated in a toilet detergent bar in concentrations as low as 0.5% exposure to ordinary daylight results in an unsightly discoloration of the bar. To attain a minimum acceptable level of deodorant effectiveness using the bisphenols in such a bar at least 2% by weight of the bisphenols has been recommended. The degree of discoloration of detergent bars containing this level of bisphenolic compounds is sufficiently great that gold or yellow coloring matter must be incorporated in the formulation for masking purposes.

Several anti-bacterial agents, although effective in aqueous solution, are incompatible with detergent actives or with high pH values generally characteristic of detergent systems. Thus, the anti-bacterial activity of phenols, for example, is almost completely lost in a soap system. Quaternary ammonium compounds are similarly incompatible with soap and anionic synthetic detergents.

It is an object of this invention to provide a composition having a high level of anti-bacterial activity.

It is a further object of this invention to provide a composition having a high level of anti-bacterial activity and reduced photosensitivity.

It is a further object of this invention to provide an anti-bacterial composition which is effective against both gram-positive and gram-negative bacteria.

It is a still further object of this invention to provide an anti-bacterial composition which is adapted to use in detergent milieu.

Other objects and improvements will become apparent from the following description and the attached drawing which graphically illustrates the surprising anti-bacterial activity attained with the combinations of this invention.

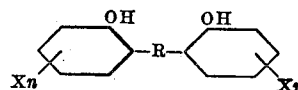
In general, this invention comprises a synergistic combination of a halogenated bisphenol and trifluoromethyl diphenyl urea. The ratio of these compounds can vary from 1:20 to 20:1, however, the preferred ratio of halogen-

2

ated bisphenol to halogenated trifluoromethyl diphenyl urea is in the range from 1:3 to 9:1. Maximum bactericidal activity occurs when the ratio of bisphenol to trifluoromethyl diphenyl urea is maintained between 1:1 and 4:1 whether the mixtures are employed in aqueous or detergent milieu.

"Synergistic combination" as used herein refers to a mixture of two or more discrete agencies which display a degree of anti-bacterial activity which is greater than the sum of the anti-bacterial activity of the agencies taken independently.

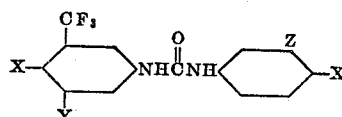
Halogenated bisphenolic compounds which find utility in this invention conform to the general structural formula:



wherein X stands for halogen, n is an integer from 1 to 3 and R represents an alkylene radical having from 1 to 4 carbon atoms, or divalent sulfur. The compounds wherein R represents an alkylene radical are more fully described in U.S. Letters Patent 2,535,077, granted December 26, 1950, as is a method for their preparation.

The preferred compounds of this general class are those which are symmetrical in structural configuration, such as bis(5-chloro-2-hydroxyphenyl) methane, bis(3,5-dichloro-2-hydroxyphenyl) methane, bis(3,5,6-trichloro-2-hydroxyphenyl) methane, bis(3,5-dichloro-2-hydroxyphenyl) sulfide, bis(3,5,6-trichloro-2-hydroxyphenyl) sulfide, and mixtures thereof.

The trifluoromethyldiphenyl urea compounds which must be used in this invention can be represented by the general structural formula:



wherein Z represents hydrogen, halogen or trifluoromethyl, X represents halogen or ethoxy, X' represents hydrogen or halogen, and Y represents hydrogen or trifluoromethyl. The preferred compounds of this group include 3-trifluoromethyl-4,4'-dichlorocarbanilide, 3-trifluoromethyl-3',4,4'-trichlorocarbanilide, 3,3'-bis(trifluoromethyl)-4-ethoxy-4'-chlorocarbanilide and mixtures thereof. These compounds are more fully described in U.S. Letters Patent 2,745,874, granted May 15, 1956.

The anti-bacterial efficacy of the synergistic combinations of this invention was established by determining their bactericidal activity in accordance with the methods developed by Cade and Halverson. (Cade, A. R., and Halverson, H. O., Soap, vol. X, #9, p. 25.) FIGURES 1 and 2 express the percent reduction in number of viable microorganisms following exposure of a suspension of either *Staphylococcus aureus* as the representative gram-positive organism or *Escherichia coli* as the representative gram-negative organism to a constant total concentration of the indicated combinations, for ten minutes at 37°C. The effectiveness of the various combinations is reflected in reduction in numbers of viable organisms.

The curves appearing in FIGURE 1 illustrate the relative bactericidal activity of varying proportions of bis(3,5-dichloro-2-hydroxyphenyl) sulfide and 3-trifluoromethyl-4,4'-dichlorocarbanilide at a constant total anti-bacterial agent concentration of 10 micrograms/ml. of solvent. The solid and broken line curves represent the percentage reduction of *S. aureus* and *E. coli*, respectively. It can be seen that neither anti-bacterial agent by itself displays significant bactericidal activity when used in 10 micrograms/ml. concentrations, while a combination comprising, for example, 7 micrograms/ml. of bis(3,5-dichloro-2-

hydroxyphenyl) sulfide and 3 micrograms/ml. of 3-trifluoromethyl-4,4'-dichlorocarbaniide results in a reduction in number of both gram-positive and gram-negative organisms of more than 80%. Synergistic anti-bacterial activity is observed throughout those portions of curves A and B in FIGURES 1 and 2 which appear above the straight lines joining the origin and terminus of the respective curves. The straight lines represent the expected values which would be obtained if the activity of the two components were merely additive.

Similarly, the curves of FIGURE 2 represent the percentage reduction of the designated test organism at varying proportions of bis(3,5,6-trichloro-2-hydroxyphenyl) methane and 3-trifluoromethyl-4,4'-dichlorocarbaniide.

The following examples are merely illustrative of the present invention and the invention is not limited to them.

Examples I to V immediately following are indicative of the synergistic anti-bacterial activity obtained by conjoint use of agents of the two classes described herein, the specific agents being fairly representative of the classes in question.

	Concentration/Micrograms per ml.		Percent Reduction	
	bis(3,5,6-Trichloro-2-hydroxyphenyl) sulfide	3-Trifluoromethyl-4,4'-dichlorocarbaniide	<i>S. aureus</i>	<i>E. coli</i>
Ex. I.....	2	8	30	34
Ex. II.....	3	7	66	36
Ex. III.....	5	5	88	65
Ex. IV.....	7	3	89	84
Ex. V.....	9	1	46	44

The activity of the mixtures of the above examples was determined in accordance with the method referred to above, i.e., sufficient anti-bacterial agent was added to a tube of FDA nutrient broth (U.S. Department of Agriculture Circular 198, December 1931, page 4) to attain the desired concentration. The suspending fluid and anti-bacterial agent were heated to 37° C. and inoculated with approximately 5,000,000 cells of the desired test organisms. These mixtures were then incubated for 10 minutes and an aliquot was removed, diluted in a 0.1% peptone water diluent, and placed on B.B.L. trypticase soy agar (supplied by Baltimore Biological Laboratories, Baltimore, Maryland). After solidification of the agar, the petri dishes were incubated for 24 hours and the number of colonies arising in that time was determined. The number of cells surviving exposure to the anti-bacterial was compared to the number contained in the original inoculum and the figure thus derived was adjusted in consideration of appropriate controls to give the percent reduction value here employed. The efficacy of the mixture of this invention in soap and non-soap synthetic detergent milieu may be observed from the following examples.

Example VI

To an aqueous solution containing 250 micrograms/ml. of white "Ivory" soap was added varying concentrations of bis(3,5-dichloro-2-hydroxyphenyl) sulfide and 3-trifluoromethyl-4,4'-dichlorocarbaniide. "Ivory" brand soap is a neutral white high grade soap consisting of a mixture of 80% sodium soap and 20% potassium soap derived from a blend of 70% tallow and 30% coconut fatty acids. Total anti-bacterial agent concentration was maintained at 5 micrograms/ml. or 2% by weight of the soap. The compositions thus prepared were tested for bactericidal activity using *S. aureus* as a representative organism and the method described supra. The following table presents the results of these tests, each value being an average of the values obtained in several runs.

Concentration/Micrograms per ml.			Percent Reduction ¹
Soap	Bisphenol	Trifluorocarbaniide	
250	5	-----	20
250	2.5	2.5	48
250	1	4	54
250	-----	5	38

¹ Derived by subtracting the percent reduction resulting from soap alone from percent reduction resulting from soap plus anti-bacterial.

The percent reduction in numbers of organisms attributable to the respective anti-bacterial agents in soap solution is comparable to the values obtained when the same agents are tested in aqueous milieu. Similar values are obtained when *E. coli* is used as the test organism. Since the anti-bacterial agent was present only in 5 micrograms/ml. concentrations in the above series the results are not directly equatable to the results obtained in aqueous milieu where the anti-bacterial agent was present in 10 micrograms/ml. concentration.

Similar results are obtained when the other anti-bacterials hereinbefore described as operable are employed in the soap matrix in place of bis(3,5-dichloro-2-hydroxyphenyl) sulfide and 3-trifluoromethyl-4,4'-dichlorocarbaniide. Further, variation of the soap matrix does not have any significant influence on the relative increase of activity attributable to the antibacterial agent.

Regular use of an "Ivory" type soap bar containing 1% of 1:1 mixture of bisphenol and halogenated trifluoromethyl diphenyl urea results in substantial reductions in the bacterial population of the skin and thus markedly reduces body odor attributable to the bacterial degradation of perspiration.

The mixtures of this invention have been found to significantly increase the anti-bacterial activity of non-soap synthetic detergent compositions. Although some of the detergents in this group, as for example alkyl benzene sulfonate, have substantial anti-bacterial effect against gram-positive microorganisms, few have significant effect against gram-negative organisms. The incorporation of a small amount of the bisphenol-halogenated trifluoromethyldiphenyl mixtures of this invention in synthetic detergent compositions will effect an increase in anti-bacterial activity against gram-positive organisms and will impart significant levels of anti-bacterial activity against gram-negative organisms.

The anionic synthetic detergent which can be employed with this invention is generally defined as a water-soluble salt of an organic sulfuric reaction product having in its molecular structure an alkyl group containing from about 8 to about 22 carbon atoms and a radical selected from the group consisting of sulfonic acid and sulfuric acid ester radicals. Important examples of the synthetics of this group which may be benefited through the incorporation therein of the mixtures of this invention, are the sodium or potassium alkyl sulfates, especially those derived by sulfation of higher alcohols produced by reduction of glycerides of tallow or coconut oil; sodium or potassium alkyl benzene sulfonates, especially those of the types described in U.S. Letters Patents 2,220,099, granted November 5, 1940, and 2,477,383, granted July 26, 1949, in which the alkyl group contains from about 9 to about 15 carbon atoms; sodium alkyl glyceryl ether sulfonates, especially those ethers in which the alkyl group is derived from the higher alcohols obtained from tallow and coconut oil; sodium coconut oil fatty acid monoglyceride sulfates and sulfonates, sodium salts of sulfuric acid esters of the reaction product of one mole of a higher fatty alcohol (e.g., tallow or coconut oil alcohols) and about three moles of ethylene oxide, and others known in the art, a number being specifically set forth in Byerly, U.S. Letters Patent 2,486,921, granted November 1, 1949, and

Strain, U.S. Letters Patent 2,486,922, granted November 1, 1949.

The nonionic synthetic detergents which are beneficially affected by the anti-bacterial mixtures of this invention may be broadly defined as compounds produced by the condensation of alkylene oxide groups with an organic hydrophobic compound which may be aliphatic or alkyl aromatic in nature.

For example, a well-known class of nonionics to which significant levels of anti-bacterial activity will be imparted through the incorporation of minor amounts of a bisphenoltrifluoromethylcarbanilide mixture is marketed under the trade name "Pluronic" by the Wyandotte Chemical Co., of Wyandotte, Michigan. These compounds are formed by condensing ethylene oxide with a hydrophobic base formed by the condensation of propylene oxide with propylene glycol.

Other nonionics which are suitable for use with the mixtures of this invention include the polyethylene oxide condensates of alkyl phenols, e.g. the condensation products of alkyl phenols having a straight or branched chain alkyl group containing from about 6 to 12 carbon atoms, with from about 10 to about 25 moles of ethylene oxide per mole of alkyl phenol. The alkyl substituent in each compound can be conveniently derived from polymerized propylene, diisobutylene, octane, or nonane or from any other natural or artificial source which will provide alkyl chains with the requisite number of carbon atoms as specified hereinbefore.

Other suitable nonionics may be derived by the condensation of ethylene oxide with the product resulting from the reaction of propylene oxide and ethylene diamine.

A minor amount of a 1:1 mixture of bis(3,5,6-trichloro-2-hydroxyphenyl) methane and 3-trifluoromethyl-4,4'-dichlorocarbanilide, for example, renders a composition containing any of the above detergents or mixtures thereof, anti-bacterially active against a broad range of microorganisms including those which are gram-negative.

Detergent compositions containing the anti-bacterial mixtures of this invention find utility in a variety of applications and physical forms as will be recognized by those skilled in the art. Such products may be used as toilet detergent bars, for example, the anti-bacterial mixture being present in amounts varying from 0.1% to 10% by weight of the total composition. Preferably, the bar would contain the said anti-bacterial mixtures in an amount varying from .5% to 2% by weight of the total composition.

Example VII

A milled toilet detergent bar was prepared in accordance with methods known and used in the art and having the following composition. "Middle-cut" as used herein refers to that fraction of coconut alcohol which consists predominantly of lauric and myristic alcohols.

	Percent
Sodium alkyl glyceryl ether sulfonate (alkyl group derived from the middle-cut of alcohols obtained by catalytic reduction of coconut oil) -----	8.0
Potassium alkyl sulfate (alkyl group derived from the middle-cut of alcohols obtained by catalytic reduction of coconut oil) -----	20.0
Magnesium soap of 80:20 tallow:coconut fatty acids -----	16.7
Sodium soap of 80:20 tallow:coconut fatty acids --	32.4
Inorganic salts -----	9.2
3-trifluoromethyl-4,4'-dichlorocarbanilide -----	1.0
Bis(3,5,6-trichloro-2-hydroxyphenyl) methane ----	1.0
Water and miscellaneous -----	11.7

A marked reduction in body odor was noted by users of this bar in a panel comparison with a control bar comprised as above, but without the antibacterial agent.

Example VIII

A granular built synthetic anionic laundry detergent composition having the following formulation was prepared by conventional means.

	Percent
Sodium alkyl benzene sulfonate (the alkyl radical averaging about 12 carbon atoms and being derived from polypropylene) -----	17.5
Sodium tripolyphosphate -----	49.7
Sodium sulfate -----	13.3
Silicate solids -----	7.0
3-trifluoromethyl-3,4,4'-trichlorocarbanilide -----	.05
Bis(3,5-dichloro-2-hydroxyphenyl) sulfide -----	.05

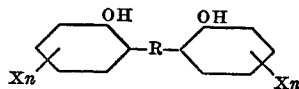
Fabrics laundered in this product were imparted with substantial levels of anti-bacterial activity as was demonstrated by a marked reduction in surviving organisms when a suspension of viable test organisms were exposed to the laundered material.

The anti-bacterial compositions of this invention may also be employed with mixtures of anionic and nonionic detergents. For example, 7.5% of a nonionic detergent agent, such as "Pluronic" can be used in conjunction with 10.0% of the sodium alkyl benzene sulfonate in the composition of Example VIII without loss of anti-bacterial activity.

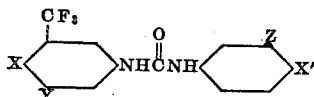
The invention has been described above in conjunction with various illustrative examples of anti-bacterial compositions, toilet and laundry detergents. It will be obvious to those skilled in the art, however, that the anti-bacterial mixtures can also be beneficially employed in such products as tooth powder, toothpaste, mouth-wash, antiseptic ointment, foot powders and the like.

What is claimed is:

1. An anti-bacterial composition comprising in combination (1) at least one halogenated bisphenolic compound having the general structural formula:



wherein X is a halogen, n is an integer of from 1 to 3, R is selected from the group consisting of an alkylene radical having from 1 to 4 carbon atoms and divalent sulfur, and (2) at least one trifluoromethyl diphenyl urea compound having the general structural formula:



wherein Z is selected from the group consisting of hydrogen, halogen, and trifluoromethyl, X is selected from the group consisting of halogen and ethoxy, X' is selected from the group consisting of hydrogen and halogen, and Y is selected from the group consisting of hydrogen and trifluoromethyl, the ratio of the said halogenated bisphenolic compound to halogenated trifluoromethyldiphenyl urea compound being between 1:20 and 20:1, the said combination displaying a synergistic anti-bacterial action when dissolved in an aqueous medium.

2. The anti-bacterial composition of claim 1 in which the said halogenated bisphenolic compound is bis(3,5,6-trichloro-2-hydroxyphenyl) methane.

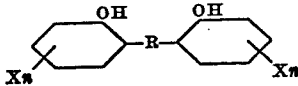
3. The anti-bacterial composition of claim 1 in which the said halogenated bisphenolic compound is bis(3,5-dichloro-2-hydroxyphenyl) sulfide.

4. The anti-bacterial composition of claim 1 in which the said halogenated trifluoromethyl diphenyl urea compound is 3-trifluoromethyl-4,4'-dichlorocarbanilide.

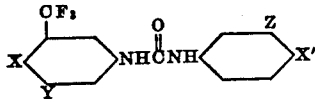
5. An anti-bacterial detergent composition comprising a surface active compound selected from the group consisting of anionic and nonionic organic detergents and mix-

7

tures thereof, and in combination a halogenated bisphenolic compound having the general structural formula:



wherein X is halogen, n is an integer of from 1 to 3 and R is selected from the group consisting of an alkylene radical having from 1 to 4 carbon atoms and divalent sulfur and a halogenated trifluoromethyldiphenyl urea compound having the general structural formula:



wherein Z is selected from the group consisting of hydrogen, halogen and trifluoromethyl, X is selected from the group consisting of halogen and ethoxy, X' is selected from the group consisting of hydrogen and halogen and X is selected from the group consisting of hydrogen or trifluoromethyl, the ratio of halogenated bisphenolic compound to halogenated trifluoromethyldiphenyl urea being between 1:20 and 20:1.

6. The anti-bacterial detergent composition of claim 5 wherein the halogenated bisphenolic compound is bis-(3,5,6-trichloro-2-hydroxyphenyl) methane.

8

7. The anti-bacterial detergent composition of claim 5 wherein the halogenated bisphenolic compound is bis-(3,5-dichloro-2-hydroxyphenyl) sulfide.

8. The anti-bacterial composition of claim 5 wherein the halogenated trifluoromethyldiphenyl urea compound is 3-trifluoromethyl-4,4'-dichlorocarbaniide.

9. An anti-bacterial detergent composition comprising a surface active compound selected from the group consisting of anionic and nonionic detergents and mixtures thereof, and in combination bis(3,5,6-trichloro-2-hydroxyphenyl) methane and 3-trifluoromethyl-4,4'-dichlorocarbaniide, the ratio of the components of said combination being between 1:1 and 4:1.

10. An anti-bacterial detergent composition comprising a surface active compound selected from the group consisting of anionic and nonionic synthetic detergents and mixtures thereof, and in combination, bis(3,5-dichloro-2-hydroxyphenyl) sulfide and 3-trifluoromethyl-4,4'-dichlorocarbaniide, the ratio of the components of the said combinations being between 1:1 and 4:1.

References Cited in the file of this patent

UNITED STATES PATENTS

2,535,077	Kunz	Dec. 26, 1950
2,745,874	Schetty	May 15, 1956