United States Patent Office 3,794,587 Patented Feb. 26, 1974

3,794,587

SYNERGISTIC ANTISEPTIC COMPOSITIONS

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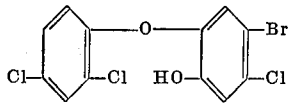
No Drawing. Continuation-in-part of abandoned application Ser. No. 63,340, Aug. 12, 1970. This application Mar. 24, 1972, Ser. No. 237,910
Int. Cl. C11d 3/48, 9/50
U.S. Cl. 252—107 5 Claims

ABSTRACT OF THE DISCLOSURE

Compositions possessing antibacterial activity through the effects of synergistic combinations of hexachlorophene and 2,4,4'-trichloro-5'-bromo-2'-hydroxydiphenyl ether.

This application is a continuation-in-part of application Ser. No. 63,340, filed Aug. 12, 1970, now abandoned.

The present invention relates to antiseptic compositions which possess synergistic activities through the effects of combinations of antibacterial agents. More specifically the present invention relates to combinations of hexachlorophene and a diphenyl ether, 2,4,4'-trichloro-5'-bromo-2'-hydroxy-diphenyl ether having the formula:



Antiseptic or antibacterial agents have been used in soaps and other detergent and cosmetic cleansing preparations for a considerable period of time. One of the most widely used of such agents has been hexachlorophene [2,2'-methylene-bis(3,4,6-trichloropheno)], as described in U.S. Pat. 2,535,077. Further, the Casely and Noel U.S. Pat. 3,177,155 discloses synergism between trihalogenated carbanilide (triclocarban) and hexachlorophene.

While hexachlorophene and the halogenated carbanilides have in general excellent properties and are widely used, they suffer certain drawbacks. Hexachlorophene is somewhat sensitive to sunlight. The substituted ureas may be unstable in alkali media at elevated temperatures. Further in order for a new antibacterial agent or system to become part of a successful product such as a toilet soap, the compounds should possess broad spectrum antibacterial activity. Such antibacterial activity should be maintained in the presence of soap or other cleansing agents. Chemical stability in the presence of the cleansing composition should be maintained, as well as non-reactivity with the other components of the cleansing composition such as perfumes, antioxidants, brighteners and the like. In addition, the product should evidence mildness and safety for general use in the finished product.

Thus relatively few antibacterial agents or bacteriostats and systems have been found which meet all of the above requirements.

In accordance with the present invention, it has been found that mixtures of hexachlorophene and 2,4,4'-trichloro-5'-bromo-2'-hydroxy-diphenyl ether exhibit synergistic antibacterial activity, and that this activity is maintained unimpaired when such mixtures are incorporated into various cleansing compositions such as soap and other detergent and cosmetic preparations. Further this synergistic activity is exhibited over very widely varying proportions of the two agents. The term "synergistic activity" as applied herein means an antibacterial effect which is greater in combination than the sum of the antibacterial effects of the separate components. The

occurrence of synergistic activity is highly unexpected and unusual.

It is therefore an object of the present invention to provide antibacterial compositions which include as antibacterial agents synergistic combinations of hexachlorophene and 2,4,4'-trichloro-5'-bromo-2'-hydroxy-diphenyl ether.

It is a further object of this invention to provide antibacterial agents which are effective in soap and in other detergent and cosmetic mediums.

It is still another object of this invention to provide antibacterial compositions which are effective over wide ratios or proportions of the antibacterial ingredients. Other objects and advantages and a fuller understanding of our invention will become apparent from the ensuing description and examples.

In a specific embodiment, our invention may be exemplified by a soap composition containing as the antibacterial agent as synergistic mixture of (A) hexachlorophene and (B) 2,4,4'-trichloro-5'-bromo-2'-hydroxydiphenyl ether and wherein the ratio of A to B present in the soap in parts by weight is about from 10 to 90 to about 90 to 10.

It is found that when components A and B of the synergistic mixture as set forth above are used together, a germicidal effect is achieved which is substantially greater than the mere total of the individual effects of the individual ingredients. Such effect is important in cases where it is desirable to increase the activity of the hexachlorophene ingredient without employing higher concentrations. Such effect is also important in cases where it is desirable to reduce the total concentration of the antibacterial agents while at the same time maintaining a desired level of antibacterial effect, or to reduce the concentration of the hexachlorophene, thereby lowering the incidents of drawbacks to the use of hexachlorophene in the product while maintaining high antibacterial effectiveness. The present invention is still further important in that this synergistic phenomena occurs even at the high pH conditions existing in detergent formulations such as soap.

The term "soap" refers to the water-soluble ammonium, phosphorus, metallic, or organic base (such as alkyl or alkoxy-alkyl containing up to about 9 carbon atoms) salts of various fatty acids or long chain synthetic acids wherein long chain refers to aliphatic radicals containing from about 12 to 22 carbon atoms. Such aliphatic radicals may be principally dodecyl, tetradecyl, hexadecyl, octadecyl; and the fatty acids may be chiefly lauric, oleic, stearic and palmetic acids. As used in this description, the term is intended to cover all products in which "soap" is a major constituent, for example bar, flake, powder, gel and liquid soap; shaving cream; toothpaste; facial and cleansing cream; and the like.

Further the "soap" ingredient may be partially, substantially or completely replaced with anionic type and nonionic type synthetic detergents. The anionic type synthetics suitable for use in the present invention can be described as those detergents having pronounced cleansing power and including in their molecular structure an alkyl radical containing from 6 to 18 carbon atoms and a sulfonic acid or sulfuric acid ester radical. Either organic base, ammonium, sodium or potassium salts of such anionic type detergents can be used. Principal types of detergents falling within this category are illustrated by alkyl-aryl sulfonates such as sodium or potassium dodecyl benzene sulfonate, sodium or potassium octadecyl benzene sulfonate, and sodium or potassium octyl naphthalene sulfonate; the alkyl sulfates such as sodium or potassium salts of dodecyl, hexadecyl, and octadecyl sulfates; the sulfonated fatty acid amides such as sodium or potassium salts of the oleic acid amide of methyl taurine; and the

sulfonated monoglycerides such as the mono-coconut oil fatty acid ester of sodium 1,2-hydroxypropane-3-sulfonate.

Suitable nonionic type synthetic detergents for use in the present invention can be described as those detergents which do not ionize in solution but owe their water-solubility to un-ionized polar groups such as hydroxy, oxyethyl or ether linkages. Principal types of detergents falling within this category are illustrated by the polyoxyethylene ethers of the higher fatty alcohols and alkyl phenols; the polyethylene glycols of fatty acid; fatty alkylol amide condensation products; polymers of ethylene and propylene oxides; compounds formed by the addition of propylene oxide to ethylene diamine followed by addition of ethylene oxide; fatty acid ethylene oxide condensation products; condensation products of ethylene oxide and a fatty acid ester of a polyhydric alcohol or sugar; and the detergents prepared by heating together a higher fatty acid with a diethanolamine. Exemplary examples of such synthetic nonionic detergents suitable for the purpose of the present invention are ethylene oxide-tall oil fatty acid reaction products; isooctyl phenol-ethylene oxide reaction products, propylene oxide-ethylene oxide reaction products; and combinations of isooctyl phenol-ethylene oxide with coconut oil or the like fatty acid ethylene oxide reaction products.

Relatively small amounts of the components of our synergistic mixtures are sufficient for the increased antibacterial effects in the detergent product. Satisfactory results can be obtained when the combined weights of the above two components are from 0.10% to 5.0% of the total weight of the detergent composition. A preferred range is a weight concentration of about 0.21% to 4.2%, and an especially preferred product is one containing soap and 0.3 to 3% combined weight of the above two components, by weight of the composition. It should be understood that even concentrations below the ranges set forth above will provide some degree of antibacterial effects, and a substantially higher concentration than those referred to will also give satisfactory results, although there are economic and other practical considerations which limit the desirability of greater amounts of the antibacterial ingredients in the soap or other medium.

As indicated above, the preferred ratios of the hexachlorophene to the diphenyl ether is about 10 to about 90 parts of the hexachlorophene to about 90 to about 10 parts of the diphenyl ether; and an especially preferred ratio of the hexachlorophene to the diphenyl ether is about 1 to about 1 part of each or 50:50 proportions.

The synergistic combination of the hexachlorophene and the 2,4,4'-trichloro-5'-bromo - 2' - hydroxy-diphenyl ether can be added to the soap and other detergents by any suitable method which results in a uniform distribution of the agents throughout the entire mass.

Specific examples illustrating our invention are set forth as follows.

EXAMPLE I

The diphenyl ether used in combination with hexachlorophene may be prepared according to the following method.

To 39 g. of potassium hydroxide containing 2 ml. of water and heated to melting was added 112 g. of 2,4-dichlorophenol. To this was added 216 g. of 3-chloro-4,6-dibromonitrobenzene. The stirred mixture was held for 2 hours at 160–170° C., cooled, and shaken with dilute potassium hydroxide solution until solid material was crystalline. The crude product was crystallized from ethanol then hydrogenated to 2'-amino-5'-bromo-2,4,4'-trichlorodiphenyl ether.

With good stirring at 40–50° C. and during a period of about 2 hours 246 g. of the diphenyl ether was added to 200 g. of 100% nitrosyl sulfuric acid dissolved in 1560 g. of concentrated sulfuric acid. After stirring at room temperature for another 3.5 hours, the mixture was cooled in an ice bath and 500 ml. of water was added slowly with vigorous stirring.

The mixture was diluted with 800 ml. of O-dichlorobenzene and boiled until no more diazonium salt was detected. While hot, the organic phase was separated and treated with about 1250 ml. of 3% sodium hydroxide solution. Solvent was steam-distilled and the residue cooled, filtered, and washed with water. Aqueous phases were combined and treated with 150 ml. of concentrated hydrochloric acid to precipitate crude 5'-bromo-2-hydroxy-2,4,4'-trichloro-diphenyl ether which, after crystallizing from ethanol, melted at 89–90° C.

EXAMPLE II

A convenient and meaningful method of measuring the antibacterial effectiveness of various agents is by means of a modified agar streak method utilizing a 10% soap solution (100,000 p.p.m. of soap) containing the various test agents. Briefly the test consists of making serial dilutions of the following solution:

10 ml. of a solution containing a specific quantity of the additive(s) in dimethyl formamide is dispensed into 80 ml. of distilled water containing 10 grams of soap. All solutions are maintained at 60° C. until they are dispensed. Aliquots of the dilutions containing concentrations of the bacteriostatic agents ranging from about 0.02 to 10 p.p.m. at 50° C. and thoroughly dispensed into measured amounts of nutrient agar. Plates are poured, allowed to solidify, and streaked with a standard 4 mm. loopful of a 24-hour broth culture of *Staphylococcus aureus* FDA 209. After incubation for 24 hours at 37° C. the bacteriostatic end point is determined. The bacteriostatic end point, hereinafter called the minimum inhibitory concentration (MIC), represents the minimum concentration in parts per million by weight of the bacteriostatic agent necessary to inhibit all growth of the innoculent organism. No particular minimum inhibitory concentration has been established to determine the usefulness of a bacteriostatic agent, although the lower the end-point, the better the bacteriostatic activity and the smaller the amount of the agent necessary to maintain a particular degree of effectiveness. The soap utilized for these evaluations was a neutral white toilet soap containing about 20% by weight of sodium coco soap and 80% by weight of sodium tallow soap.

Using the modified agar streak method as set forth above bacteriostatic effectiveness of a soap solution containing 1% of each of hexachlorophene and the diphenyl ether alone, in 50/50 proportions and in 5:1 proportions was determined. The results are set forth in Table I.

TABLE I

Bacteriostat	Minimum expected MIC, no synergism	MIC versus *S. aures* found (p.p.m.)
1% 2,4,4'-trichloro-5'-bromo-2'-hydroxy diphenyl ether		[1] 0.14–0.16
1% hexachlorophene		0.34–0.38
0.5% 2,4,4'-trichloro-5'-bromo-2'-hydroxy diphenyl ether; plus, 0.5% hexchlorophene	[2] 0.20	0.12
0.167% 2,4,4'-trichloro-5'-bromo-2'-hydroxy-diphenyl ether; plus 0.833% hexachlorophene	[2] 0.30	0.16

[1] Partial inhibition.
[2] Based on MIC of 0.14 for the dipenyl ether and 0.38 for the hexachlorophene.

EXAMPLE III

Using the modified agar streak method set forth above, additional results illustrating varying proportions of hexachlorophene and 2,4,4' - trichloro-5'-bromo-2'-hydroxy-diphenyl ether are set forth in Table II. From the results in Table II, it may be seen that effective synergism exists in the range from about 10:90 to about 90:10 of hexachlorophene:diphenyl ether. All of the evaluations shown in Table II were run in the same day to avoid day-to-day variations in bacteriological testing.

TABLE II

Ratio of 1% hexachlorophene to 1% 2,4,4'-trichloro-5'-bromo-2'-hydroxy-diphenyl ether	Expected MIC, no synergism	Minimum inhibitory concentration versus *S. aureus* (p.p.m.)
100:0	----------	0.18
90:10	0.198	0.16
80:20	0.126	0.12
70:30	0.23	0.09
60:40	0.25	0.09
50:50	0.27	0.10
40:60	0.29	0.10
30:70	0.31	0.12
20:80	0.32	0.14
10:90	0.34	0.20
0:100	----------	0.36

The results set forth in the foregoing examples with respect to a specific soap (20% sodium coco and 80% sodium tallow soap) are obtained with soaps generally. Thus, a fatty acid soap such as sodium laurate, potassium stearate, sodium oleate, and potassium myristate will also produce these results. Furthermore, the synergistic action is independent of the soap medium and will take place in non-detergent media as well as in anionic detergents other than soap and in nonionic detergent systems. At the same time, soap is a system in which the synergistic components are highly effective and useful.

While this invention has been described and exemplified in terms of its preferred embodiments, those skilled in the art will appreciate that variations and modifications may be made without departing from the spirit and scope of the invention.

What is claimed is:

1. Antiseptic compositions consisting essentially of a cleansing composition selected from the group consisting

of water soluble soaps, nonionic synthetic organic detergents, and anionic synthetic organic detergents and a synergistic combination of hexachlorophene and 2,4,4'-trichloro-5'-bromo-2'-hydroxy-diphenyl ether wherein the ratio of said hexachlorophene to said diphenyl ether in parts by weight is from about 10:90 to about 90:10 and wherein the total concentration of said combination is from about 0.1% to about 5% of the total weight of the composition.

2. An antiseptic composition according to claim **1** wherein the ratio of the hexachlorophene to the diphenyl ether is about 50:50.

3. An antiseptic composition according to claim **1** wherein said cleansing composition is a water-soluble soap.

4. An antiseptic composition according to claim **1** wherein said cleansing composition is an anionic synthetic organic detergent.

5. An antiseptic composition according to claim **1** wherein said cleansing composition is a nonionic synthetic organic detergent.

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U.S. Cl. X.R.

252—106; 424—340, 347