

2,739,941

GERMICIDAL SOAP COMPOSITION

Max E. Chiddix, Easton, and Stanley H. Hesse, Bethlehem, Pa., assignors to General Aniline & Film Corporation, New York, N. Y., a corporation of Delaware

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5 Claims. (Cl. 252—107)

This invention relates to a new class of halogenated alkylidenebis nitrophenols possessing very strong germicidal and fungicidal properties.

The problem of finding a germicide effective in soaps is an old one. Early investigators tried organic mercurials as well as mercuric salts in soap, but these compounds are toxic and irritating. The germicide added to soaps, particularly to toilet soaps, should fulfill the following conditions in addition to retaining its germicidal powers:

(1) It should not react with soap constituents and with the moisture contained in the soap.

(2) It should not be influenced by the free alkali of the soap nor by the alkalinity produced by the hydrolysis of the soap in water.

(3) It should not be volatile and should not have a disagreeable odor.

(4) It should be relatively non-toxic, should not be irritating to the skin, or be a sensitizer.

During the development of this subject and the nature of the problems involved, it became manifest that very few chemicals will meet these requirements. Of the many chemical compounds investigated, substituted phenols, such as alkyl phenols, aryl phenols, and halogenated phenols showed effective germicidal properties at high concentration in soap, but lost their effectiveness at a concentration of 5% or lower. A probable explanation is that phenols form alkali salts or addition products with the soap and that such compounds possess little bactericidal action.

In the search for phenolic substances which would not be influenced by the alkali of the soap, W. S. Gump United States Patents 2,250,480, 2,272,268, 2,353,724, 2,353,735, 2,354,012 and 2,354,013 found a number of diphenols which retained a large part of their bactericidal strength in the presence of excessive amounts of soap, and thus became practical for the formulation of germicidal soaps. These active phenols are derivatives of diphenyl, diphenylsulfide, and diphenylmethane, such as:

2,2'-dihydroxy-3,5,3',5'-tetrachlorodiphenyl

2,2'-dihydroxy-3,5,6-3',5',6'-hexachlorodiphenylsulfide

2,2'-dihydroxy-3,5,6-3',5',6'-hexachlorodiphenylmethane.

When these substances are added to soap, only one of the two hydroxy groups is apparently neutralized, forming monoalkali metal salts and leaving the remaining hydroxy group free. This may account, at least in part, for the bactericidal activity of these phenols in the presence of alkaline-reacting soap.

On the basis of the evidence presented by Gump and by numerous other investigators in this field, a number of generalizations can be formulated, to wit:

The introduction of halogen into the nucleus of a phenolic compound without exception increases its bactericidal potency. This increase is less for the ortho-position than the para, perhaps owing to interaction between the hydroxyl groups and halogen atoms. Little evidence is available for meta-compounds. The effect of halogen substitution, in general, increases with increas-

ing atomic weight of the halogen. However, the effect of iodine has been little studied.

The introduction of an alkyl group into the phenol nucleus produces a rise in bactericidal action, followed by a decrease as the carbon chain extends beyond 5 or 6 carbon atoms when *E. Typhosa* and other gram-negative organisms are employed for testing. For *Staph. Aureus* and other gram-positive varieties, the increase in activity continues somewhat irregularly until the compound becomes too insoluble to test satisfactorily. A normal carbon chain has more effect than a branched one containing the same number of carbon atoms. A primary alkyl group has more effect than a secondary or tertiary alkyl group of the same weight. A given number of carbon atoms produces more effect in a single side chain than when distributed between two or more. The effect of halogen and alkyl on bactericidal properties is more or less independent, i. e., if an alkyl group raises the phenol coefficient a halogen atom increases it still further.

The effect of introducing an alkyl group into a hydroxy-biphenyl or hydroxydiphenylmethane is irregular and unpredictable.

Separation of an alkyl group from the phenol nucleus by oxygen decreases the germicidal activity, and the presence of oxygen as an alcohol or ether group in the side chain likewise produces this effect. On the other hand, a sulfur atom between the aryl and alkyl group increases the bactericidal action, the sulfur acting somewhat as an additional methylene group.

Increasing the number of hydroxyl groups attached to an aromatic nucleus decreases the germicidal activity, a decrease that cannot effectively be compensated for by alkyl and halogen when more than two hydroxyl groups are present.

The introduction of a nitro group or the replacement of a chlorine atom by a nitro group in a chlorinated phenol nucleus decreases the germicidal activity especially in compounds of the type of 2,2'-methylenebis-4,6-dichlorophenol. Although 2,2'-methylenebis-4-nitrophenol and 2,2'-methylenebis-4-nitro-6-chlorophenol possess some germicidal activity, it is not, however, sufficient to warrant their use as germicides in soaps. The bactericidal properties of the latter two phenols in soap mixtures were very inferior as will be shown hereinafter.

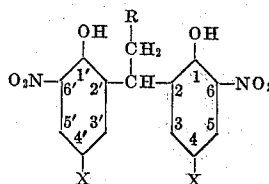
We have found that certain halogenated alkylidenebis nitrophenols, contrary to the teachings of the prior art, exhibit an unusual bactericidal strength when added to soaps and are, therefore, of great practical value for the preparation of antiseptic soaps.

Accordingly, it is an object of the present invention to provide a new class of halogenated alkylidenebis nitrophenols which do not react with soap constituents, are not rendered ineffective by the free alkali of the soap nor by the alkalinity produced by the hydrolysis of the soap in water, are not volatile, have no disagreeable odor, and are relatively non-toxic.

A further object is to provide a new composition of matter in the form of a germicidal soap.

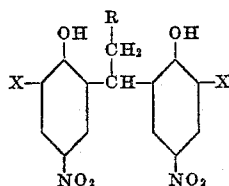
Other objects and advantages will appear hereinafter.

The compounds having the foregoing properties and which are very effective against *Micrococcus pyogenes* var. *aureus* in the presence of soaps are characterized by the following general formulae:



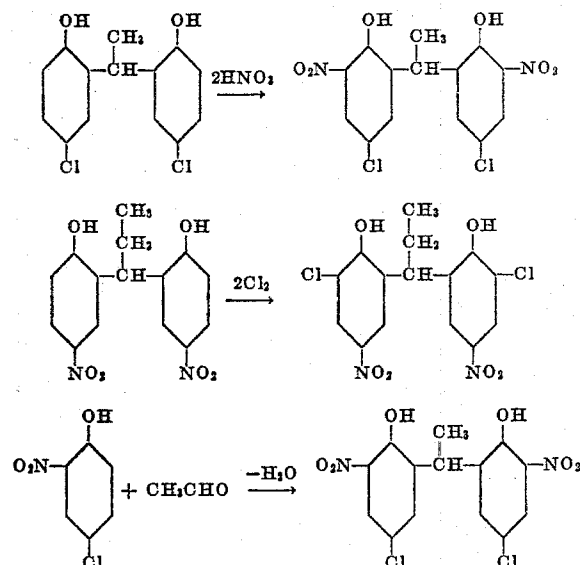
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and



wherein R represents either hydrogen, methyl, ethyl, chloromethyl, or trichloromethyl group, and X represents a halogen, such as bromine, chlorine, or iodine.

These compounds are prepared by the conventional nitration of the halogenated bisphenol, by the halogenation of the dinitrophenol, or by direct condensation of an aldehyde or aldehyde yielding substance with the appropriate phenol according to the following reactions:



These compounds are not only effective as germicides in soaps but also as fungicides and antiseptics. They may also be used in cosmetics, skin lotions, deodorants, detergents, detergent bars and shampoos. From our experimental work, we have obtained sufficient evidence to attribute the excellent bactericidal properties of these compounds to the chain length of the carbon atoms in the alkylidene bridge. Methylenebis compounds are comparatively ineffective as germicides in soap. By increasing the number of carbon atoms from 1 to 2 and as high as 4, the bactericidal property is unexpectedly increased. The presence of the nitro group either in the 4- or 6-, including 4'- or 6'-, position instead of chloro also contributes to the unexpected bactericidal properties. In fact, the compounds of the present invention are four times more effective than 2,2'-methylenebis-4-nitrophenol, 2,2'-methylenebis-4-nitro-6-chlorophenol, and 2,2'-methylenebis-4-chloro-6-nitrophenol.

Examples of halogenated bisphenols which may be nitrated are:

2,2'-ethylidenebis-4-chlorophenol
2,2'-ethylidenebis-4-bromophenol
2,2'-ethylidenebis-4-iodophenol
2,2'-propylidenebis-4-bromophenol
2,2'-propylidenebis-4-chlorophenol.

Examples of dinitrophenols which may be halogenated are:

2,2'-ethylidenebis-4-nitrophenol
2,2'-propylidenebis-4-nitrophenol
2,2'-ethylidenebis-6-nitrophenol
2,2'-butylidenebis-6-nitrophenol.

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Examples of phenols and aldehydes or aldehyde yielding substances which may be condensed to form the desired compounds are:

- 5 2-chloro-4-nitrophenol
- 2-bromo-4-nitrophenol
- 2-iodo-4-nitrophenol
- 2-nitro-4-chlorophenol
- 2-nitro-4-bromophenol, and
- 10 2-nitro-4-iodophenol with the following:

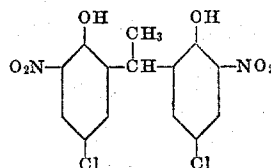
Acetaldehyde
Paraldehyde
Propionaldehyde
Butyraldehyde
Chloral
15 Chloroacetaldehyde
Dimethyl acetal
Chlorodimethyl acetal
Diethyl acetal.

- 20 The following examples describe in detail the methods for accomplishing the above objects. It is to be understood, however, that they are inserted merely for purposes of illustration and are not to be construed as limiting the scope of the invention.

- 25 It is to be further noted that the compounds illustrated according to Examples 3 to 6 inclusive are not within the purview of the compounds characterized by the foregoing general formula but are merely inserted for purposes of comparison.

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EXAMPLE 1



2,2'-ethylidenebis-4-chloro-6-nitrophenol

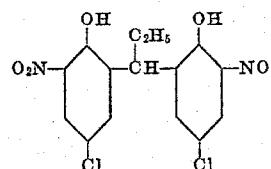
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- 40 28.3 grams (0.1 mole) of 2,2'-ethylidenebis-p-chlorophenol, prepared according to the method disclosed in Example 1 of our application Serial No. 272,688, filed on February 20, 1952, were suspended in 200 ml. of glacial acetic acid in a 250 ml, three-necked flask equipped with a stirrer, dropping funnel, and thermometer. At room temperature 13.6 ml. of fuming nitric acid were added dropwise in about 1½ hours while maintaining the temperature at 25° C. by cooling on occasion with an ice bath. Addition of the acid caused complete solution. When the addition was complete, the reaction mixture was stirred at 25° C. for an additional 1½ hours. After stirring for about ½ hour, a fine yellow precipitate began to separate. The reaction mixture was drowned on ice and the yellow precipitate was filtered off by suction. The crude product was dried overnight at 50° C. to give 34 grams of product (92% of the theoretical yield) which melted at 144–150° C. The crude product was crystallized from 100 ml. of acetic acid. The crystals were washed with low boiling petroleum ether to give 14 grams of product which melted at 161–163° C.

Anal.—Calculated for $C_{14}H_{10}O_6N_2Cl_2$: N, 7.51. Found: N, 7.37.

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EXAMPLE 2



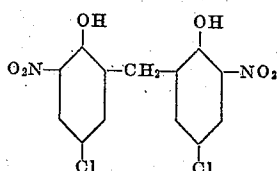
2,2'-propylidenebis-4-chloro-6-nitrophenol

- 70 29.7 grams (0.1 mole) of 2,2'-propylidenebis-p-chlorophenol, prepared from p-chlorophenol and propionaldehyde according to the procedure disclosed in our applica-
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tion Serial No. 272,688, filed on February 20, 1952, were suspended in 200 ml. of glacial acetic acid in a 250 ml., three-necked flask equipped with a stirrer, dropping funnel, and thermometer. At room temperature 13.6 grams of fuming nitric acid were added dropwise in about 1½ hours while maintaining the temperature at 25° C. by cooling on occasion with an ice bath. When the addition was complete, the reaction mixture was stirred at 25° C. for an additional 1½ hours. It was then drowned on ice and the yellow precipitate was filtered off by suction. The crude product was dried overnight at 50° C. and then crystallized from 100 ml. of acetic acid to give 31 grams of product (80% of the theoretical yield) which melted at 118–121° C. Recrystallization from 50 ml. of acetic acid gave 25.5 grams of product which melted at 120–121.5° C. A third crystallization gave a product which melted at 122–122.5° C.

Anal.—Calculated for $C_{15}H_{12}O_6N_2Cl_2$: N, 7.24. Found: N, 7.44.

EXAMPLE 3

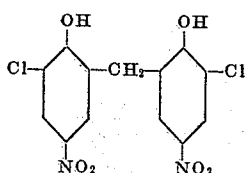


2,2'-methylenebis-4-chloro-6-nitrophenol

70 grams (0.25 mole) of 2,2'-methylenebis-p-chlorophenol were suspended in 550 ml. of glacial acetic acid in a one-liter, three-necked flask equipped with a stirrer, dropping funnel, and thermometer. At room temperature, 34 grams of fuming nitric acid were added dropwise in about 1½ hours, while maintaining the temperature at 25° C. When the addition was complete, the reaction mixture was stirred at 25° C. for an additional 1½ hours. It was then drowned on ice and the yellow precipitate was filtered off by suction. The crude product was pressed as dry as possible and crystallized from 1,200 ml. of acetic acid. There were obtained 47 grams of product (52% of the theoretical yield) which melted at 178–179° C.

This compound is reported in the Journal of the American Chemical Society, 72, 837 (1950) as melting at 181–182° C.

EXAMPLE 4

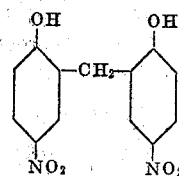


2,2'-methylenebis-4-nitro-6-chlorophenol

200 grams of concentrated sulfuric acid were placed in a 250 ml., three-necked flask equipped with a stirrer, thermometer, and dropping funnel. To this were added 34.7 grams (0.2 mole) of 2-chloro-4-nitrophenol in small portions, while maintaining the temperature at 10° C. by cooling. When the addition was complete, it was stirred for an additional hour at 10° C., but solution was still incomplete. 7.5 grams (0.1 mole) of 40% formaldehyde solution were then added dropwise in an hour at 10° C. When addition was complete, the reaction mixture was stirred an hour at 20° C. and then the temperature was gradually raised to 60° C. After a few minutes at 60° C., the reaction mixture turned to an almost solid mass. Heating was stopped at once. The reaction mixture was cooled as rapidly as possible and drowned on ice. The white precipitate was filtered off by suction, washed acid free, and dried at 50° C. overnight to give 35 grams of product (97% of the theoretical yield) which melted at 266–284° C. A sample was crystallized from acetic acid to give light yellow needles which melted at 284° C. with decomposition.

Anal.—Calculated for $C_{13}H_8O_6N_2Cl_2$: N, 7.80. Found: N, 8.30, 8.39.

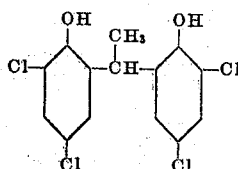
EXAMPLE 5



2,2'-methylenebis-4-nitrophenol

400 grams of concentrated sulfuric acid were placed in a 500 ml., three-necked flask equipped with a stirrer, dropping funnel, and thermometer. To this were added 112 grams (0.8 mole) of p-nitrophenol in small portions while maintaining the temperature at 10° C. by cooling. The addition required about 2 hours. When the addition was complete, it was stirred for an additional hour at 10° C. and solution was only partial. 30 grams (0.4 mole) of 40% formaldehyde solution were then added dropwise at 10° C. When the addition was complete, the reaction mixture was stirred an hour at 20° C. and then the temperature was gradually raised to 45° C. when the reaction mixture solidified. The reaction flask was then placed in a water bath at 60° C. and allowed to stand until the temperature had dropped back to that of the room. The pasty material was removed, slurried in ice water, and filtered by suction. The crude product was washed until acid free. Considerable difficulty was encountered with attempts to crystallize the crude product from ethanol and dilute methanol, due to the impurity of the p-nitrophenol. After considerable loss, 14 grams of crude product were finally obtained. This was crystallized from 100 ml. of nitrobenzene to give 7.5 grams of a yellow crystalline product which melted at 266° C. with decomposition. The compound is reported in *Frdl.* 3, 77 as melting at 231° C. with decomposition.

EXAMPLE 6

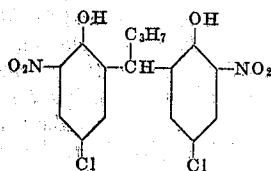


2,2'-ethyldienebis-4,6-dichlorophenol

84.9 grams (0.3 mole) of 2,2'-ethyldienebis-p-chlorophenol were dissolved in 400 ml. of glacial acetic acid in a 500 ml., three-necked flask equipped with a stirrer, thermometer, and gas inlet and outlet tube. At 10° C., 43.5 grams of chlorine were introduced in 2 hours. The reaction mixture was drowned on ice and allowed to stand overnight. The oil which had originally separated became crystalline by standing. After drying at 50° C., the crude product was crystallized from 150 ml. toluene to give 52.5 grams of product which melted at 108–110° C.

Anal.—Calculated for $C_{14}H_{10}O_2Cl_4$: Cl, 40.29; OH, 2.00. Found: Cl, 41.01; OH, 2.03.

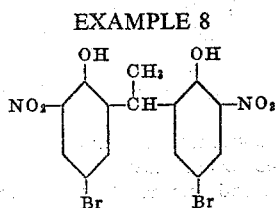
EXAMPLE 7



2,2'-butyldienebis-4-chloro-6-nitrophenol

31.1 grams (0.1 mole) of 2,2'-butyldienebis-p-chlorophenol, prepared from p-chlorophenol and butyraldehyde

according to Example 1 of our aforesaid application, were suspended in 200 ml. of glacial acetic acid in a 250 ml., three-necked flask equipped with a stirrer, dropping funnel, and thermometer. This compound was nitrated by the addition of 13.6 grams of fuming nitric acid in the same manner as Example 1. The crude product was purified by crystallization from acetic acid.



2,2'-ethylidenebis-4-bromo-6-nitrophenol

37.2 grams (0.1 mole) of 2,2'-ethylidenebis-p-bromophenol, prepared from p-bromophenol and paraldehyde according to Example 1 of our aforesaid pending application, were suspended in 200 ml. of glacial acetic acid in a 250 ml., three-necked flask equipped with a stirrer, dropping funnel, and thermometer. This compound was nitrated by the addition of 13.6 grams of fuming nitric acid at 25° C. in the same manner as Example 1. The crude product was crystallized from acetic acid.

2,2'-alkylidenebis-4-nitro-6-chlorophenols prepared by condensing acetaldehyde, propionaldehyde, and the like with 2-chloro-4-nitrophenols in the presence of sulfuric acid gave practically the same bactericidal results as the corresponding 4-chloro-6-nitrophenol isomers. From these experiments, it became apparent that it made no difference whether the chloro-nitro groups were either in the 4- or 6-position, respectively, so long as a nitro group was present in each of the aryl nuclei.

The compounds of the present invention were found to have unusually high bactericidal killing power when tested by the following method. This test which was used to evaluate the various compounds as a soap germicide measures the ability of the sample to kill bacteria. With this test, the following materials were employed:

- (1) Soap—4% solution of soap granules (Ivory soap); germicide at a concentration of 2% of soap or 0.08% in the solution.
- (2) Difco Bacto-nutrient agar.
- (3) F. D. A. (U. S. Food & Drug Administration) nutrient broth.
- (4) Tryptone-glucose extract agar.

The organism employed was *Staphylococcus aureus* 209 (now known officially as *Micrococcus pyogenes* var. aureus, Bergey VI) which was maintained on tryptone-glucose extract agar. Three consecutive transfers were made from this stock culture in F. D. A. broth at 24-hour intervals. The third transfer was used and contained about 500,000,000 organisms per ml.

Sterile contact tubes containing 10 ml. of the soap-germicide solution were placed in a 37° C. water bath and permitted to reach temperature. One ml. of the test organism culture was added to each tube and mixed well. After 5 minutes' contact at 37° C., one ml. was removed from each contact tube and diluted to 100 ml. with sterile distilled water. Since a number of tests were run at the same time, this dilution usually stood for about 15 to 20 minutes before further dilution and plating.

Dilutions of 1-1,000 and 1-10,000 were plated in nutrient agar. The plates were incubated for 48 hours at 37° C. and then counted. The numbers reported were those bacteria remaining alive from the original 1 ml. sample which was removed from the contact tube. All tests were run in duplicate.

The test results obtained are shown in the following table.

Table 1

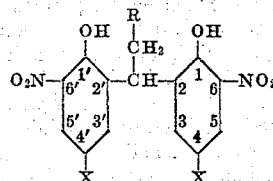
Compound	Bactericidal Test
2,2'-ethylidenebis-4-chloro-6-nitrophenol.....	84,000
2,2'-propylidenebis-4-chloro-6-nitrophenol.....	62,000
2,2'-methylenebis-4-chloro-6-nitrophenol.....	260,000
2,2'-methylenebis-4-nitro-6-chlorophenol.....	340,000
2,2'-methylenebis-4-nitrophenol.....	550,000
2,2'-ethylidenebis-4,6-dichlorophenol.....	550,000
2,2'-butylidenebis-4-chloro-6-nitrophenol.....	74,000
2,2'-ethylidenebis-4-bromo-6-nitrophenol.....	76,000

From the foregoing table, it is clearly evident that using the compounds of Examples 1, 2, 7, and 8 only one-third to one-fourth as many bacteria remained alive as in the case of the compounds of the remaining examples.

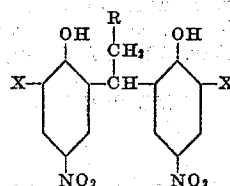
The germicidal compounds of the present invention may be added to any soap in any suitable manner during the crutching or milling or similar operation. The concentration of the germicidal compound in such soap may range from 0.5 to 5% based on the weight of the soap. The nature of the soap is immaterial so long as it is used as a cleansing or detergent agent and is employed for the washing of the human body, dishes, or laundry articles.

We claim:

1. A germicidal soap composition consisting of a detergent soap and 0.5 to 5.0% by weight of a halogenated alkylidenebis nitrophenol selected from the group consisting of those of the following formulae:

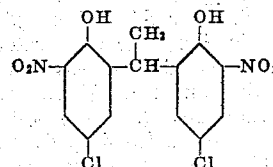


40 and

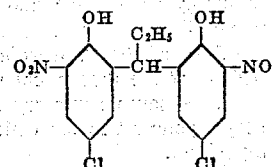


- 50 wherein R is selected from the group consisting of hydrogen, methyl, ethyl, chloromethyl, and trichloromethyl groups, and X represents a halogen selected from the group consisting of chlorine, bromine and iodine.

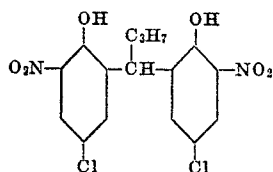
- 55 2. A germicidal soap consisting of a detergent soap and 0.5 to 5.0% by weight of 2,2'-ethylidenebis-4-chloro-6-nitrophenol having the following formula:



- 65 3. A germicidal soap consisting of a detergent soap and 0.5 to 5.0% by weight of 2,2'-propylidenebis-4-chloro-6-nitrophenol having the following formula:



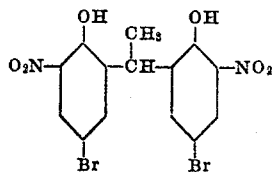
4. A germicidal soap consisting of a detergent soap and 0.5 to 5.0% by weight of 2,2'-butylidenebis-4-chloro-6-nitrophenol having the following formula:



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5. A germicidal soap consisting of a detergent soap and 0.5 to 5.0% by weight of 2,2'-ethylidenebis-4-bromo-6-nitrophenol having the following formula:



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