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HALOGENATED PHENOXY DIPHENYL PHOSPHINIC ACIDS AND SALTS THEREOF

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ABSTRACT OF THE DISCLOSURE

(Halogenated phenoxy) diphenyl phosphinic acids and salts thereof useful as bacteriostatic agents, are disclosed. The disclosed compounds, such as [p-(p-bromo-phenoxy) phenyl]-phosphinic acid and its alkali metal and ammonium salts, are especially useful as the active ingredients in germicidal detergent compositions.

This invention relates to the control of bacterial growth, and more particularly, to bacteriostatic agents and to germicidal detergent compositions containing said agents.

The search for commercially desirable bacteriostatic agents which are compatible with and useful in detergent compositions is a continuing one. The popularity of detergent compositions, for both laundry and toilet use, containing germicidal agents has increased tremendously over the past few years. It is presently estimated that more than 20% of the toilet bar soap sales are now of products containing a germicidal agent, and this percentage is steadily increasing. While numerous substances have been investigated for use in detergent compositions, few are found desirable as commercial bacteriostatic agents in detergents. In many cases, the bacteriostatic agent is chemically incompatible with the detergent; in other cases, its germicidal activity is abated when the bacteriostat is conjoined with the detergent composition.

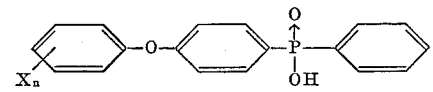
We have discovered a new class of compounds, useful as bacteriostatic agents, which are compatible with detergent compositions and which exhibit germicidal activity in the detergent compositions.

Therefore, it is an object of this invention to provide new compounds which are useful as bacteriostatic agents. Another object of this invention is to provide new germicidal agents which are compatible with detergent compositions and which maintain this activity even when incorporated into detergent compositions. Other objects and advantages will appear as the specification proceeds.

One aspect of the present invention lies in the discovery that certain (halogenated phenoxy) diphenyl phosphinic acids and their alkali metal and ammonium salts have definite antibacterial properties, and that these properties increase markedly in the presence of an alkaline agent such as a detergent or soap.

In a specific embodiment, our invention may be exemplified by an antiseptic detergent composition comprising a detergent and a germicidally effective amount of an alkali metal salt or an ammonium salt of a (halo-

genated phenoxy) diphenyl phosphinic acid having the structure:



wherein X is a halogen such as chlorine and bromine, and n is an integer from 1 to 3. Particularly effective bacteriostatic results have been obtained where X is bromine, although the extent of such effectiveness varies somewhat according to the degree of halogenation and the spacial relationship of the halogen groups. Preferably, the halogen group or groups should be located in the meta or para positions rather than in the ortho positions. The degree of halogenation may vary and although monohalogenated compounds are preferred, di- and tri-halogenated compounds show bacteriostatic effects.

Small amounts of our diphenyl phosphinic acid compounds are sufficient to make a detergent composition antiseptic. The amount to be used in a particular instance will vary over a wide range depending upon such factors as the degree of effectiveness desired, the particular diphenyl phosphinic acid compound employed and the economics involved. Generally, from about 0.2% to about 5% based on the weight of the total detergent composition, will provide desirable antiseptic effect. It should be understood that lesser or greater amounts are operable but without substantial advantages. A preferred range, in a detergent composition such as soap, is an amount in the order of from about 0.5% to about 3%.

Bacteriostatic agents represented by the general formula given above may be prepared by reacting a bis-(substituted phenyl) ether with phenylphosphorous dichloride in the presence of aluminum trichloride, at temperatures in the range of about 80° to 120° C. and reaction times approximating 24 hours, then adding the reaction mixture to water. This reaction results in partial dehalogenation and formation of monobasic, chloroform insoluble and chloroform soluble, phosphorus acid fractions. The desired reaction fraction is the chloroform soluble monobasic phosphorous acid, which forms water-soluble alkali and ammonium salts.

In order to more fully describe the nature of the compositions of the present invention and the manner in which they may be used, the following illustrative specific examples are provided:

EXAMPLE I

Phenyl[p-(p-Bromophenoxy) phenyl]-phosphinic acid is prepared as follows:

To a solution of 32.8 grams (0.1 mole) of bis(p-bromophenyl) ether in 30 ml. of perchloroethylene, was added 17.9 grams (0.1 mole) of phenylphosphorous dichloride and 17 g. (0.12 mole) of aluminum trichloride. Anhydrous conditions were maintained. The mixture was heated under reflux (124° C.) with agitation for 22 hours and then poured onto 800 grams of crushed ice with stirring. After warming to room temperature, the aqueous layer was separated and the organic portion (a brown oil) was dissolved in dichloromethane and washed 5

times with water. Upon standing overnight, the brown solid which precipitated from the organic portion was filtered off, washed with dichloromethane, boiled in one l. of chloroform, and filtered while hot. The residue was dissolved in aqueous sodium hydroxide and filtered to clear it of turbidity, then reprecipitated with hydrocholoric acid, filtered off, washed, and dried. It weighed 10 grams and had the following analysis:

	Percent Phosphorus	Percent Bromine	Acid/P, Molar ratio	Br/P, Molar ratio
$CHCl_3$, insoluble	4.2	15.4	1.67	1.41

The chloroform filtrate was evaporated to one-fifth of its volume and cooled to −20° C. The white precipitate of phenyl-[p-(p-Bromophenoxy) phenyl]-phosphonic acid which resulted was filtered off, washed with cold acetone, and vacuum-dried. The dried diphenyl phosphinic acid weighed 12 grams (31% yield) and had a melting point of 202–7° C.

Analysis:

Bromine calculated for $C_{18}H_{14}BrPO_3$: 20.55%. Found: 22.0%.

Phosphorus calculated: 7.96%. Found: 8.0%.

Acid equivalent weight calculated: 389.2%. Found: 389%.

The chloroform soluble fraction was identified by its phosphorous and bromine analysis, acid equivalent, and infrared spectrum as phenyl-[p-(p-Bromophenoxy) phenyl]-phosphinic acid. It is a wide, crystalline solid, monobasic acid which forms water-soluble alkali salts.

The alkali metal salt was obtained by reacting the diphenyl phosphinic acid with a strong alkali metal hydroxide such as sodium or potassium hydroxide or the like. Formation of the alkali metal or ammonium salt is desirable for convenience and ease of incorporating the diphenyl phosphinic acid into a detergent such as soap.

EXAMPLE II

Germicidal activity of the sodium salt of the phenyl-[p-(p-Bromophenoxy) phenyl]-phosphinic acid prepared in Example I was determined by both a modified agar streak method utilizing a soap solution and by a tube dilution technique utilizing a broth as follows:

For the agar streak dilution method, the sodium salt was dissolved in a suitable solvent at a 1.0% level. Suspensions in a 10% soap solution were then prepared. The soap utilized was a neutral white toilet soap containing about 20% by weight of sodium coco soap and about 80% by weight of sodium tallow soap. The concentration of the diphenyl phosphinic acid salt in the soap solution was 1,000 p.p.m., or 0.1%. Thereafter, serial dilutions were made containing 100 p.p.m. and 10 p.p.m. Aliquot amounts of the test solutions were thoroughly dispersed into measured amounts of sterile liquid nutrient agar so as to obtain concentrations of the diphenyl phosphinic acid salt ranging from .05 to 100 p.p.m. Plates were then poured, allowed to solidify, and streaked with a standard 4 mm. loopful of a 24-hour broth culture of *S. aureus* FDA 209 or with *E. coli*. After incubation for 24 hours at 37° C., the bacteriostatic endpoint was determined. The bacteriostatic endpoint represents the minimum concentration in p.p.m. of the bacteriostatic agent necessary to completely inhibit all growth of the inoculum.

The tube dilution test was performed by making serial dilutions of the diphenyl phosphinic acid salt solution in nutrient broth, ranging from 0.01 to 500 p.p.m. Then the tubes were inoculated with 0.05 ml. of a 24-hour broth culture of *S. aureus* FDA 209 or of *E. coli* and incubated at 37° C. for 24 hours. The minimum inhibitory concentration was then determined.

The minimum inhibitory concentration endpoints for completely inhibiting all bacterial growth are set forth in Table I. It will be noted that the activity of the bacteriostatic agent increased in the presence of the soap.

TABLE I.—MINIMUM CONCENTRATION FOR INHIBITING BACTERIAL GROWTH (P.P.M.)

Phenyl-[p-(p-Bromophenoxy) phenyl]-phosphinic acid (sodium salt)	*S. aureus*	*E. coli*
In broth	>100	>500
In soap	10	100

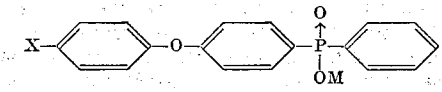
When the diphenyl phosphniic acids were tested for bacterial growth inhibition in an alkaline environment such as alkali metal or ammonium detergents, the minimum inhibitory concentrations were the same as those given for the sodium salts of the acid in the table above. Other substitutions, besides the bromine substitution, may be made without destroying bacteriostatic activity.

The results obtained above with respect to bacteriostatic activity in the specific soap above (20/80 sodium salts of coco/tallow fatty acids) are obtained with soaps generally. The activity exhibited by these compounds is independent of the soap vehicle. and other alkaline media may be used, such as anionic and non-ionic type synthetic detergents. At the same time, soap is a system in which the compounds are highly effective. "Soap" refers to the water-soluble metallic, ammonium, or organic base salts of various fatty acids, such as lard, lauric, oleic, myristic, palmitic, stearic, and the like.

While this invention has been described with respect to certain embodiments, it is not so limited; and it is to be understood that variations and modifications thereof, obvious to those skilled in the art, may be made without departing from the spirit or scope of our invention.

What is claimed is:

1. (Halogenated phenoxy) diphenyl phosphinic acids and salts of the structure:



wherein X is a halogen selected from the group consisting of chlorine and bromine and M is selected from the group consisting of hydrogen, alkali metal and NH_4.

2. Phenyl - [p-(p-Bromophenoxy) phenyl]-phosphinic acid.

3. The compounds of claim **1** wherein M is sodium.

4. The compounds of claim **1** wherein M is potassium.

5. The compounds of claim **1** wherein M is NH_4.

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