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QUATERNARY AMMONIUM SALTS OF ORGANOPHOSPHORUS ACIDS

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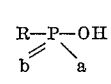
The object of the present invention is the preparation of microbiologically active compounds by the reaction of certain quaternary ammonium hydroxides or their salts of inorganic acids with organophophorus acids or their water-soluble salts. The phrase "organophosphorus acids" here refers to acids containing at least one phosphorus-carbon bond. Alkyl and aryl phosphonic, phosphonous, phosphinous and phosphinic acids exemplify this type of compound. The quaternary ammonium compounds used in the process of this invention contain at least one carbon chain having from eight to twenty-two carbon atoms and the quaternary nitrogen atom may be a member of a heterocyclic ring such as pyridine, isoquinoline, morpholine or pyrrolidine, if desired.

The preparation of alkyl phosphonic acids has been described by Kosolapoff and Weber in JACS 68 2540–41 (1946). Alkyl phosphinic and alkyl phosphonous acid preparations are described in U.S.P. 2,686,803. Aryl phosphonous acid preparations are described in J. Chem. Soc. 1955 2039–40 by Maguire and Shaw. Aryl phosphinic acid preparations are described by Higgins et al. in JACS 77 1864–6 (1955) and aryl phosphonic acids have been prepared by Lecher et al. in JACS 76 1045–51 (1954). Phosphinous acids are described by Robins in J. Org. Chem. 16 324–7 (1951).

As suitable structures in this application we may employ a wide variety of derivatives including paraffinic, olefinic, aromatic and heterocyclic organophosphorus acids or their alkali metal, ammonium or other water-soluble salts as well as functional derivatives of these compounds containing halogen, amino, nitro or sulfur containing substituents.

A general formula for the phosphorus acids of this application is:



where R is a substituted or unsubstituted alkyl or aryl radical, *a* is OH, H or R' (a hydrocarbon radical which may or may not be the same as R) and *b* is either oxygen when P has a valence of 5 ("ic" acids) or is not present when P has a valence of 3 ("ous" acids). In general the total number of carbon atoms in R plus R' will be from six to thirty.

Typical examples of the quaternary ammonium compounds which may be used in this invention are the alkyl trimethyl ammonium chlorides, alkyl-benzyl trimethyl ammonium chlorides, alkyl dimethyl-benzyl ammonium chlorides, alkyl dimethyl menaphthyl ammonium chlorides, alkyl dimethyl substituted-benzyl ammonium chlorides in which the benzyl radical is substituted with one or more side chains containing from one to five carbon atoms such, for example, as methyl, dimethyl, ethyl and the like and in which the carbon atoms may all be in the same or different side chains or in which the benzyl radical bears one, two or more halogen atoms such as chlorine or bromine, alkyl pyridinium chlorides, alkyl isoquinolinium chlorides and bromides, alkyl lower-alkyl pyrrolidium chlorides, alkyl lower-alkyl morpholinium chlorides in all of which the alkyl group may have from eight to twenty-two carbon atoms and the lower alkyl group may have from one to four carbon atoms and alkyl phenoxy ethoxy ethyl dimethyl-benzyl ammonium chloride in which the alkyl radical may be iso-octyl or nonyl and in which the phenyl radical may, if desired, be substituted by a methyl radical. Various other analogs of these quaternaries may also be employed such, for example, as cetyl dimethyl ethyl ammonium bromide or oleyl dimethyl ethyl ammonium bromide.

In general, the quaternary ammonium compounds useful in this invention are the higher alkyl quaternary ammonium hydroxides, halides, (chlorides and bromides), sulfates, methosulfates and the like possessing the following formula:

where R is an alkyl or alkaralkyl radical containing from eight to twenty-two carbon atoms or an alkyl phenoxy ethoxy ethyl radical in which R is an alkyl radical containing from eight to nine carbon atoms and in which the phenyl radical may be substituted by a methyl group; R' and R'' are methyl or ethyl radicals or members of a heterocyclic ring system such as pyridine, isoquinoline, pyrrolidine and morpholine; R''' is a methyl radical or a benzyl group or a substituted-benzyl group such, for example, as a monochlorobenzyl radical or a dichlorobenzyl radical or mixture thereof or a methyl benzyl, dimethyl benzyl, ethyl benzyl, diethyl benzyl, isopropyl benzyl, tertiary butyl benzyl or another benzyl radical containing from one to five carbon atoms as side chains, either as a single side chain or a multiplicity of side chains including mixtures thereof or a menaphthyl group or hydroganated menaphthyl group. When R' and R'' are members of a morpholine or pyrrolidine ring, R''' is a methyl, ethyl, propyl, or butyl group. When R' and R'' are members of an unsaturated heterocyclic ring such as pyridine or isoquinoline, R''' is the same radical as R''. X in the above formula corresponds to a halide radical such as chloride, bromide or iodide or to any other water-soluble anion such as methosulfate.

In general, we prefer to use such quaternary ammonium compounds which have a phenol coefficient of at least 100 with respect to both *Staphylococcus aureus* and *Salmonella typhosa* at 20° C. when determined by the standard method given in the "Official Methods of Analysis of the Association of Official Agricultural Chemists," Ninth Edition (1960), page 63 et seq.

The compounds of this invention may be prepared by mixing aqueous solutions of the quaternary ammonium salts or hydroxides with an aqueous solution of the acid in question or any of its water-soluble salts.

After thorough mixing, the organic product layer is separated from the aqueous layer (as with a separatory funnel) since two distinct phases are formed. Separation may be facilitated by the addition of an organic solvent immiscible with water. The product layer may be washed with water to remove any residual by-product salt or unreacted materials. The solvent, if any, may be evaporated and the product air or vacuum dried to a paste, wax, oil or solid.

It is not necessary to use an aqueous medium. Any solvent or solvent mixture in which the starting materials are soluble will be satisfactory. Non-aqueous solvents facilitate the separation of by-product inorganic salt and reduce the need for vacuum drying to get an anhydrous product. When a non-aqueous medium is employed, it is usually necessary to add a small amount of water to facilitate ionic reaction.

The product may be used, if desired, without drying since any entrapped water is irrelevant to the microbiological activity of the compounds. In other applica-

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tions, removal of water may be essential for reasons not related to biological activity.

An alternate method for the preparation of compounds especially applicable to the treatment of fabric, ropes, net, woven and non-woven fabric and reticulated or convoluted materials, involves a two-step process. In the first step, the material is passed through a bath containing the anionic moiety. Excess solution is removed by methods well known to those skilled in the art. The treated material is then passed through a second bath wherein the concentration of quaternary ammonium compound is such that the material pickup will result in an equivalent amount of quaternary ammonium compound reacting with the anionic moiety, depositing the product in the most intimate way on the surface and in the interstices, convolutions and reticulations of the material.

The method of adjustment of solution concentration to achieve the required pickup is well known to those skilled in the art. The order of treatment may be reversed without affecting the biological activity or durability of the product on the material. The products of this invention may be formulated as water dispersions by dissolving them in a water-miscible organic solvent such as acetone or methanol and diluting with water or by dissolving them in emulsifiable oils such as, for example, sulfonated castor oil or pine oil and diluting with water. In preparing aqueous dispersions, emulsifying agents such, for example, as ethylene oxide condensates of alkyl phenols may be used with or without organic solvents.

It is surprising that the compounds of this invention exhibit high microbiological activity despite their relative insolubility in water. Because of their usual combination of physical and microbiological properties, they can be used to impart laundry-resistant anti-microbial characteristics to textiles. They can also be used as the active agent in antimildew finishes for textiles which are resistant to leaching with water.

Although the compounds have low water solubility, they are compatible with various organic solvents, plasticizers and high molecular weight compounds. Consequently, they may be incorporated as anti-microbial agents in synthetic resins and plastics. The compounds are compatible with natural and synthetic rubber latices. Therefore, they may be used to prepare bacteriostatic films and molded objects deposited from such latices.

The compounds can be incorporated into cutting and grinding fluids without precipitation. Also, they blend well with non-ionic and anionic surface active agents. In such compositions they retain their microbiological activity.

It will be understood that the properties of the products described herein will vary depending upon the nature of the cationic quaternary ammonium compound used in their preparation as well as the anionic compound reacted therewith.

The chemical, physical and biological properties of the products of our invention make them especially appropriate for the following applications when suitably incorporated in active amounts in an appropriate vehicle, binder, medium or substrate:

(1) Mildewproofing fabric, canvas, ropes, textiles, awnings, sails, tenting and other woven and non-woven reticulated materials.

(2) Paint mildewstats.

(3) Jet plane fuel additive to control growth of microorganisms.

(4) Odor preservative agents for clothes and shoes.

(5) Mildew retardant and odor suppressant for shoes and other leather products.

(6) Topical antiseptics.

(7) Antidandruff agents.

(8) Disinfection agents for hair and gut of man and beast.

(9) Bacteriostatic furniture dressing.

(10) Surface finishes for stone, plaster, tile, cement, brick and other inorganic building materials, to retard growth of microorganisms, fungi, mold and algae.

(11) Wool preservative.

(12) Plant and tree spray to combat fungi.

(13) Antimycotic agents for soap wrappers.

(14) Self-sanitizing brushes.

(15) Mildewproofing agent in and on plastic and film.

(16) Mildewproofing of cellulosics, cardboard, fibreboard, paper and cordage.

(17) Contact biostat for application to film, waxes and cloth to preserve cheese, meats and vegetables and other food products.

(18) Algal inhibition, especially on surfaces and in solution where low foaming is desirable.

(19) Paper pulp slime control.

(20) Sanitizing agent for rug, carpet, curtains.

(21) Egg preservation.

(22) Adhesive preservation.

(23) Preservation of latex paints.

(24) Preservation of metal-working compounds.

(25) Additives for soap and for both anionic and non-ionic detergents in liquid, bar, powder, bead, solution and other forms to impart bacteriostatic and fungistatic properties thereto.

The microbiological activity of our compounds has been evaluated for microbiological stasis by the Standard Tube Dilution Test, the technique for which is common knowledge to those skilled in the art. A Difco Bacto CSMA Broth #0826 was used in the study. This test is used to determine the lowest concentration of microbiologically active compounds which will inhibit the growth of the organism in question. For a wide range of applications, the inhibition of growth rather than outright kill is satisfactory.

Briefly put, the Tube Dilution Test consists in placing 9 cc. of the CSMA Broth in a test tube which is then sterilized in an autoclave. One cc. solution of the microbiologically active compound at an appropriate concentration is added to the test tube which is then inoculated with 0.1 cc. of a twenty-four hour old culture of the organisms under study. The test tube is then incubated at 37° C. for forty-eight hours and observed for bacterial growth.

The same procedure is followed for fungi. In such tests, however, the tubes are incubated for fourteen days at a temperature suitable for optimum fungal growth, usually 25° C.

The invention is illustrated by, but not restricted to, the following examples:

Example I

A stock solution containing 0.61 m./liter of the sodium salt of benzene phosphinic acid was prepared. To 60 grams of this solution in a 250 ml. separatory funnel was added 120 grams of a 10% solution of alkyl dimethyl ethyl-benzyl ammonium chloride (Onyx Chemical Corporation, BTC–471; alkyl distribution: C_{12} 50%, C_{14} 30%, C_{16} 17%, C_{18} 3%). The funnel was shaken and 50 cc. of benzene added to facilitate layer separation. The organic layer was separated and the benzene evaporated on a steam bath. The product was vacuum dried to give 16.5 grams of a yellow paste (98% yield).

Example II

To and additional 60 grams of the stock solution described in Example I was added 120 grams of a 10% solution of alkyl dimethyl-benzyl ammonium chloride (Onyx Chemical Corporation, BTC–824; alkyl distribution: C_{14} 60%, C_{16} 30%, C_{12} 5%, C_{18} 5%). The mixture was poured into a separatory funnel, benzene added and the funnel well shaken. The organic product layer was separated and dried first on a steam bath and then in a vacuum oven to give a white paste (17.5 grams) in 100% yield.

Example III

To an additional 60 grams of the stock solution described in Example I was added 120 grams of a 10% solution of lauryl isoquinolinium bromide (Onyx Chemical Corporation, Isothan Q–75). The mixture was stirred with benzene and then poured into a separatory funnel to permit layer separation. The organic product layer was dried first on a steam bath and finally in a vacuum oven to give 16.1 grams (87% yield) of a dark brown paste.

Example IV

Six grams of the disodium salt of benzene phosphonic acid was used to prepare a 10% aqueous solution and this was mixed with 130 grams of a 10% solution of lauryl isoquinolinium bromide identical to that used in Example III. The product was worked up as in Example III to give 13 grams (71% yield) of a dark brown paste.

The microbiological activity of the products of this invention is illustrated in Table I which shows results obtained by means of the Standard Tube Dilution Test described above. The performance of the products listed in this table was determined with respect to *Staphylococcus aureus* (*S.a.*), *Salmonella typhosa* (*S.t.*) and *Aspergillus niger* (*A.n.*).

TABLE I

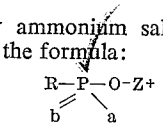
Product from Example	Reciprocal of Static Dilution of Product vs—		
	S.a.	*S.t.*	*A.n.*
I	10^6	10^6	10^6
II	10^6	10^6	10^5
III	10^6	10^5	10^5
IV	10^6	10^5	10^5

Standard Tube Dilution tests carried out with the product of Example I showed static dilution levels of 1/75,000 against both *Penicillium luteum* and *Pullalaria pullulans*.

In addition, the product from Example I was an effective biocide against *Ceratocytis ulmi* at 1000 p.p.m.

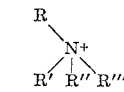
We claim:

1. A quaternary ammonium salt of an organophosphorus acid having the formula:



wherein R is selected from the group consisting of alkyl and aryl; "*a*" is selected from the group consisting of OH, H, alkyl and aryl; and "*b*" represents oxygen when P has a valence of 5 and is not present when P has a valence of 3; and Z^+ is the cation of a quaternary ammonium compound having a phenol coefficient of at least 100.

2. The compound as defined in claim 1 wherein the quaternary ammonium cation has the formula:



wherein R is selected from the group consisting of an alkyl having from 8 to 22 carbon atoms, an alkaralkyl having from 8 to 22 carbon atoms, an alkyl phenoxyethoxyethyl in which the alkyl group has from 8 to 9 carbon atoms and in which the phenyl is unsubstituted or substituted by a methyl group; R′ and R″ are selected from the group consisting of methyl, ethyl, and when together as part of a heterocyclic ring selected from the group of pyrrolidine and morpholine; and R‴ is selected from the group consisting of methyl, benzyl and a substituted benzyl, or along with R′ and R″ is part of a heterocyclic ring selected from the group of pyridine and isoquinoline.

3. The compound as defined in claim 1 in which Z^+ is an alkyl-benzyl trimethyl ammonium cation in which the alkyl has from 8 to 22 carbon atoms.

4. Alkyl dimethyl ethyl-benzyl ammonium benzene phosphinate wherein alkyl contains from 8 to 22 carbon atoms.

5. Alkyl dimethyl benzyl ammonium phosphinate wherein the alkyl group has 8 to 22 carbon atoms.

6. Lauryl isoquinolinium benzene phosphinate.

7. Di(lauryl isoquinolinium) benzene phosphonate.

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