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QUATERNARY AMMONIUM AROMATIC AMINO SULFONATES

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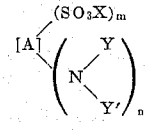
The object of the present invention is the preparation of microbiologically active compounds by reaction of certain quaternary ammonium hydroxides or their salts of inorganic acids with aromatic amino sulfonic acids or their salts, and substituted aromatic amino sulfonic acids containing chlorine, bromine, or hydroxyl groups attached to the aromatic nucleus.

The quaternary ammonium compounds used in the process of this invention contain at least one carbon chain having from 8 to 22 carbon atoms. The quaternary nitrogen atom may be a member of a five- or six-membered heterocyclic ring such as pyridine, isoquinoline, morpholine, or pyrrolidine if desired.

Typical examples of these quaternary ammonium compounds are 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 1 to 4 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 lower alkyl pyrrolidinium chlorides, alkyl lower alkyl morpholinium chlorides in all of which the alkyl group may have from 8 to 22 carbon atoms and the lower alkyl group may have from 1 to 4 carbon atoms and alkyl phenoxy ethyl dimethyl benzyl ammonium chloride in which the alkyl radical may be isooctyl or nonyl and in which the phenyl radical may, if desired, contain a substituent 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.

It has generally been thought that microbiologically active quaternary ammonium compounds of the preceding types are not compatible—i.e., lose their microbiological activity—in the presence of anionic materials, particularly anionic surface active agents such as soaps.

We have found, however, that contrary to general belief the reaction of microbiologically active water-soluble quaternary ammonium compounds with aromatic amino sulfonic acids of the aforementioned types, or with water-soluble salts of such acids, yields products which in many cases are equally as active microbiologically as the parent quaternary ammonium compounds from which they are derived. In many cases they are more active.



wherein A is an aromatic hydrocarbon nucleus containing from 6 to 14 carbon atoms and possessing at least one single or condensed benzene ring system, X is hydrogen, an alkali metal, NH_4, or other anion of a water-soluble ionizable salt of the aforesaid sulfonic acid, Y and Y′ are H or lower alkyl radicals containing from 1 to 4 carbon atoms, and *m* and *n* are small whole numbers between 1 and 4, and wherein both the SO_3X and



groups are nuclear substituents and wherein A may also contain other nuclear substituted groups such as chloro-, bromo-, iodo-, or hydroxyl radicals.

As suitable aromatic amino sulfonic acids we may mention o-amino benzene sulfonic acid, p-amino benzene sulfonic acid, m-amino benzene sulfonic acid and substituted amino benzene sulfonic acid containing ring-substituted chlorine, bromine, or hydroxyl radicals such, for example, as o-amino phenol-p-sulfonic acid, amino naphthol sulfonic acids such, for example, as 1-amino-2-naphthol-4-sulfonic acid and its various isomers, 2-amino-naphthalene-1-sulfonic acid, 4-amino-naphthalene-1-sulfonic acid, 3-amino-naphthalene-1-sulfonic acid, 4-methylamino-naphthalene-1-sulfonic acid, 5-amino-naphthalene-1-sulfonic acid and the like including their chloro, bromo, and hydroxy-substituted derivatives. We may also use more complex aromatic amino sulfonic acids such, for example, as 4,4′-diamino stilbene-disulfonic acid. Where more than one acidic hydrogen is present in the molecule, as for example in disulfonic acids or hydroxyl sulfonic acids, either one or all of the acidic hydrogens from either sulfonic acid radicals or hydroxyl groups may be converted to the form of quaternary ammonium salts.

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 8 to 22 carbon atoms or an alkyl phenoxy ethoxy ethyl radical in which R is an alkyl radical containing from 8 to 9 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 1 to 4 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 hydrogenated 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 of the anions hereinabove listed, such as methosulfate.

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

An alternative 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 unusual 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 anti-mildew 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 quaternary ammonium compound used in their preparation as well as the aromatic amino sulfonic acid or salt 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.

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 microbiological 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 organism 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 was prepared containing 10 weight percent of the sodium salt of metanilic acid. To a vigorously agitated aliquot of this solution containing 0.294 equivalent weight of the compound was added the chemical equivalent weight of a 10 weight percent solution of alkyl dimethyl ethyl benzyl ammonium chloride in which the alkyl distribution is 50% C_{12}, 30% C_{14}, 17% C_{16}, 3% C_{18} (BTC–471 manufactured by the Onyx Chemical Corporation). The agitated mixture was poured into a separatory funnel. The mixture separated into two phases. The organic product layer was removed and vacuum dried to yield a brown paste of alkyl dimethyl ethyl benzyl ammonium metanilate in 87.6 percent theoretical yield.

When dissolved in sopropanol and added to fuel oil to the extent of 1250 parts per million, this product prevented the growth of bacteria in contaminated oil.

Biostasis of this product was evaluated against *Staphylococcus aureus, Salmonella typhosa, Aspergillus niger,* and *Trichophyton interdigitale* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:1,000,000; *S. typhosa,* 1:1,000,000; *A. niger,* 1:100,000; *T. interdigitale,* 1:500,000.

Example II

An aliquot of the stock solution in Example I containing 0.067 equivalent of sodium metanilate was vigorously agitated while a chemical equivalent amount of alkyl dimethyl benzyl ammonium chloride (Onyx Chemical Corporation, BTC–824, in which the alkyl radical corresponds to 60% C_{14}, 30% C_{16}, 5% C_{12}, and 5% C_{18}) in the form of a 10 weight percent solution was slowly added. The organic product was removed and vacuum dried to yield alkyl dimethyl benzyl ammonium metanilate as a gray solid in 92.5 percent theoretical yield.

Biostasis of this product was evaluated against *Staphylococcus aureus, Salmonella typhosa, Aspergillus niger,* and *Tricophyton interdigitale* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:1,000,000; *S. typhosa,* 1:100,000; *A. niger,* 1:100,000; *T. interdigitale,* 1:500,000.

Example III

An aliquot of the stock solution in Example I containing 0.067 equivalent of sodium metanilate was vigorously agitated while a chemical equivalent amount of lauryl isoquinolinium bromide (Onyx Chemical Corporation, Isothan Q–75) in the form of a 10 weight percent solution was slowly added. The agitated mixture was then poured into a separatory funnel. The mixture separated into two phases. The organic product layer was removed and the product was vacuum dried to yield a dark brown paste of lauryl isoquinolinium metanilate in 81.5 percent theoretical yield.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described aabove. The product showed biostasis at the dilutions shown: *S. aureus,* 1:1,000,000; *S. typhosa,* 1:100,000; *A. niger,* 1:100,000.

Example IV

A stock solution was prepared containing 10 weight percent of the sodium salt of sulfanilic acid. To a vigorously agitated aliquot of this solution containing 0.0315 equivalent weights of the compound was added the chemical equivalent weight of a 10 weight percent solution of the alkyl dimethyl ethyl benzyl ammonium chloride of Example I. The agitated mixture was poured into a separatory funnel. The mixture separated into two phases. The organic product layer was removed and vacuum dried to yield an alkyl dimethyl ethyl benzyl ammonium sulfanilate as a yellow paste in 78 percent theoretical yield.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:100,000; *S. typhosa,* 1:100,000; *A. niger,* 1:10,000.

Example V

An aliquot of the stock solution in Example I containing 0.0315 equivalent of sodium sulfanilate was vigorously agitated while a chemical equivalent amount of the alkyl dimethyl benzyl ammonium chloride of Example II in the form of a 10 weight percent solution was slowly added. The agitated mixture was then poured into a separatory funnel. The mixture separated into two phases. The organic product layer was removed and vacuum dried to yield a yellow paste of alkyl dimethyl benzyl ammonium sulfanilate in 81 percent theoretical yield.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:10,000,000; *S. typhosa,* 1:100,000; *A. niger,* 1:100,000.

Example VI

An aliquot of the stock solution in Example I containing 0.308 equivalent of sodium sulfanilate was vigorously agitated while a chemical equivalent amount of lauryl isoquinolinium bromide of Example III in the form of a 10 weight percent solution was slowly added. Benzene was added to the agitated mixture which was then poured into a separatory funnel. The mixture separated into two phases. The organic product layer was removed and the benzene evaporated on a steam bath. The product was vacuum dried to yield lauryl isoquinolinium sulfanilate as a dark red paste in 87 percent theoretical yield.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standdard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:10,000,000; *S. typhosa,* 1:1000,000; *A. niger,* 1:100,000.

This product, when incorporated in soap at the 2% level, resulted in a bacteriostatic soap showing activity against *Staphylococcus aureus* comparable to that of hexachlorophene in a hand-washing test.

The product of this example was also found effective in the control of dandruff when incorporated in shampoos.

Example VII

Two tenths part of the product of Example VI and 99.8 parts of a commercial grade of gypsum joint cement containing no mold inhibitor were blended and pasted up with sufficient water to make a heavy dough which was applied by spatula to a 3-inch by 6-inch piece of fibreboard.

Another fibreboard sample was coated with the same gypsum joint cement paste containing no inhibitor.

Both samples, after hardening, were placed in a desiccator with the bottom covered with water and out of reach of the samples. A moldy piece of gypsum-coated fibreboard was placed in the desiccator which was then closed. Within three days, the untreated sample showed heavy mold growth, whereas the sample containing the product of Example VI was completely barren of such growth after two weeks.

Example VIII

In a 500 ml. separatory funnel were placed 100 grams of a 10% solution of the sodium salt of 1-amino-2-naphthol-4-sulfonic acid and 145 grams of a 10% solution of the alkyl dimethyl ethyl benzyl ammonium chloride of Example I. The funnel was well shaken and then 50 ml. of benzene added to facilitate layer separation. The product layer was separated, the benzene evaporated on a steam bath and then placed in a vacuum oven to dry. The product was a black paste of alkyl dimethyl ethyl benzyl ammonium 1-amino-2-naphthol-4-sulfonate (20 grams—88% yield).

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:100,000,000; *S. typhosa,* 1:100,000,000; *A. niger,* 1:10,000.

Example IX

Using the technique of Example VIII above, the sodium salt of 1-amino-2-naphthol-4-sulfonic acid was reacted with a chemically equivalent amount of the alkyl dimethyl benzyl ammonium chloride of Example II. The product, alkyl dimethyl benzyl ammonium 1-amino-2-

naphthol-4-sulfonate, was a black solid and was obtained in 94% yield.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:100,000; *S. typhosa,* 1:100,000; *A. niger,* 1:10,000.

Example X

In a 1 liter separatory funnel were placed 330 grams of a 10% solution of the disodium salt of 4,4'-diamino stilbene-2,2'-disulfonic acid and 220 grams of alkyl dimethyl ethyl benzyl ammonium chloride identical to that used in Example VIII above. Using the technique of Example VIII, 30 grams of a yellow solid (70% yield) was obtained.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:1,000,000; *S. typhosa,* 1:100,000; *A. niger,* 1:100,000.

In a similar manner, the 4,4'-diamino stilbene-2,2'-disulfonic acid was reacted with alkyl dimethyl benzyl ammonium chloride (identical to that used in Example IX above). The product was a yellow solid obtained in 81% yield.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:1,000,000; *S. typhosa,* 1:1,000,000; *A. niger,* 1:100,000.

Using the same technique, the lauryl isoquinolinium bromide of Example III was reacted with an equimolar quantity of 4,4'-diamino stilbene-2,2'-disulfonic acid to give a red powder in 86% yield.

All three of these products were quaternary ammonium salts of the diamino stilbene disulfonic acid. By a similar technique, using the mono sodium salt and only one mole equivalent of quaternary, the corresponding monosalts may be made.

Example XI

In a 500 ml. separatory funnel were placed 180 grams of a 10% solution of alkyl dimethyl ethyl benzyl ammonium chloride (identical to that used in Example VIII) and 60 grams of a 10% solution of the disodium salt of o-amino phenol-p-sulfonic acid. The funnel was well shaken and then layer separation allowed to occur. The product layer was dried in a vacuum oven to give 22.5 grams (98% yield) of a dark brown paste. This product was the salt of alkyl dimethyl ethyl benzyl ammonium chloride and o-amino phenol-p-sulfonic acid in which both hydroxyl and sulfonic acid groups were converted to their corresponding quaternary ammonium salts.

Biostasis was evaluated against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger* by the Standard Tube Dilution Test described above. The product showed biostasis at the dilutions as given: *S. aureus,* 1:1,000,000; *S. typhosa,* 1:1,000,000; *A. niger,* 1:100,000.

Example XII

A 25 weight percent solution of the product of Example II was prepared in ethylene glycol mono butyl ether and mixed with a commercial grade of alkyd base paint containing no other fungicide in the ratio of 4 parts by weight of this solution to 96 parts by weight of paint. Strips of filter paper cut to 1 inch by 4 inches were coated with this paint and allowed to dry. They were then inoculated with a culture of *Pullularia pallulans* and held in an incubator at 25° C. and 90% relative humidity for three weeks. At the end of this time, no fungus growth was visible.

Example XIII

Four parts of the 25% solution of the product of Example II prepared according to Example III were added to 96 parts of a latex acrylic type paint with thorough stirring and the latex emulsion thus treated was inoculated with a culture of *Pullularia pallulans* and incubated as in Example XII. At the end of three weeks, no fungus growth was visible in the latex.

In general, the products of this invention are useful in the control of plant diseases and plant pests. They exhibit little or no phytotoxicity when dipped or sprayed onto plant foliage in the form of 0.1% active solutions or dispersions. Thus, for example, there is no phytotoxicity observed by application of such concentrations of the product of Example II to Wood's Prolific Lima Beans, whereas such application affords marked control of Mexican bean beetles feeding on the foliage.

We claim:

1. A quaternary ammonium aromatic amino sulfonate in which the quaternary nitrogen atom is linked to at least one straight-chain alkyl having 12 to 18 carbon atoms.

2. Alkyl dimethyl ethyl-benzyl ammonium metanilate in which the alkyl has 12 to 18 carbon atoms.

3. Lauryl isoquinolinium metanilate.

4. Alkyl dimethyl benzyl ammonium metanilate in which the alkyl has 12 to 18 carbon atoms.

5. Alkyl dimethyl ethyl-benzyl-ammonium 1-amino-2-naphthol-4-sulfonate in which the alkyl has 12 to 18 carbon atoms.

6. Di(alkyl dimethyl ethyl-benzyl ammonium) 4,4'-diaminostilbene-2,2'-disulfonate in which the alkyl radical has 12 to 18 carbon atoms.

7. Di(alkyl dimethyl ethyl-benzyl ammonium)-o-aminophenylate-p-sulfonate in which the alkyl has 12 to 18 carbon atoms.

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