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2,700,683

ALKYLATED BENZYL, LAURYL, DIMETHYLAMMONIUM HYDROXIDE AND SALTS THEREOF

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This invention relates to antimicrobial substances and specifically to quaternary ammonium compounds that show high antimicrobial activity. The present application is in part a continuation of copending application Serial No. 144,378, filed February 15, 1950, now U. S. Patent No. 2,676,986.

The antimicrobial activity of quaternary ammonium compounds has been known for some time as is evidenced by U. S. Patent No. 2,108,765, granted February 15, 1938, to Domagk. These compounds have come into fairly wide use as antiseptic agents, but unfortunately, commercially available compounds do not exhibit an activity as high as is known to be obtainable.

Thus Lawrence et al. have reported in an article in the Journal of the American Pharmaceutical Association, Volume 36, No. 51, pages 353 to 358 (November 1947), the phenol coefficients of several (alkyl, benzyl, dimethyl) ammonium chlorides as follows:

Phenol coefficients of alkyl dimethyl benzyl ammonium chlorides

[Phenol coefficient at 20° C.]

Alkyl group	<i>Staphylococcus aureus</i>	<i>Salmonella typhosa</i>
Hexyl.....	Less than 16.....	Less than 11.....
Octyl.....	Less than 16.....	Less than 11.....
Decyl.....	50.....	55.....
Dodecyl.....	214.....	150.....
Tetradecyl.....	600.....	450.....
Hexadecyl.....	214.....	150.....
Octadecyl.....	50.....	66.....

It is accordingly clear that quaternary ammonium compounds could be made to have the high activity shown by Lawrence et al. for the (tetradecyl, benzyl, dimethyl) ammonium chloride if the tetradecyl radical could be readily incorporated at a reasonable cost. However, this radical is most readily provided by myristic acid, which occurs only in small quantities in some relatively scarce fats and oils and is therefore not easily available in commercial quantities. For this reason the most widely used prior commercial quaternary antimicrobial compounds has been the dodecyl, benzyl, dimethyl ammonium chloride referred to by Lawrence et al., the dodecyl radical being readily available commercially from lauric acid which is found in large quantities in coconut oil. In actual manufacture the prior art preparation is somewhat more effective than indicated in the Lawrence et al. article. This is apparently because natural lauric acid normally contains appreciable quantities of the normal 10-, 14- and 16-carbon acids in addition to the 12-carbon acid, and the natural acid is used without separation of these materials. In general about a fifty per cent increase in phenol coefficient can be contributed by this factor.

Among the objects of the present invention is the provision of improved commercially attractive quaternary ammonium compounds having higher antimicrobial activity than the commercial preparation heretofore available.

The above, as well as additional objects of the present

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invention, will be more readily understood from the following description of exemplifications thereof.

It has been discovered that antimicrobial activities approximating or exceeding the maximum shown by Lawrence et al., can be readily provided in commercially feasible quaternary benzyl, n-dodecyl, dimethyl, ammonium compounds where the benzyl ring is substituted with at least one alkyl group, and the total number of carbon atoms in the group or groups so substituted is between two and four.

Representative compounds of the above new type are as follows:

- (2,4-dimethyl benzyl, lauryl, dimethyl) ammonium chloride
- (3,4-dimethyl benzyl, lauryl, dimethyl) ammonium chloride
- (Ar-ethyl benzyl, n-dodecyl, dimethyl) ammonium chloride
- (Ar-n butyl benzyl, n-dodecyl, dimethyl) ammonium chloride
- (Ar-tertiaryl-butyl benzyl, lauryl, dimethyl) ammonium chloride
- (Ar-trimethyl benzyl, n-dodecyl, dimethyl) ammonium chloride
- (Ar-tetramethyl benzyl, n-dodecyl, dimethyl) ammonium chloride
- (Ar-diethyl benzyl, n-dodecyl, dimethyl) ammonium chloride
- (Ar-secondary butyl benzyl, n-dodecyl, dimethyl) ammonium chloride

as well as the corresponding bromides and free quaternary ammonium hydroxides. In fact, the compounds of the present invention include salts of the above cations with any water-solution anion although for pharmaceutical use anions of non-toxic water-soluble acids are preferred. Further examples of non-toxic acids are the mineral acids, including nitric acid, sulphuric acid, orthophosphoric acid, metaphosphoric acid, pyrophosphoric acid, phosphorous acid, and the acids recited in the above-mentioned Domagk patent, including the organic acids ethyl sulfuric acid, formic acid, acetic acid, lactic acid, tartaric acid, citric acid, benzene sulfonic acid, p-toluene sulfonic acid, benzoic acid and salicylic acid.

In addition to the above, corresponding compounds in which the benzene ring has one or two of its hydrogens substituted by chlorine atoms are also highly effective. In fact, such a substitution generally increases the activity of the above compounds by about one third. Corresponding compounds having bromine and iodine substituted in place of the chlorine show even higher activities. On the other hand, substitution of fluorine in place of the chlorine usually results in a slight lowering of activity.

The following is an example of how one of the above compounds is prepared:

(Ar-ethyl-benzyl, lauryl, dimethyl) ammonium chloride

Thirty-eight grams (0.25 mol) of Ar-ethyl-benzyl chloride (an isomeric mixture prepared by chloromethylating ethyl-benzene) and 61 grams (0.25 mol) of lauryl dimethyl amine were mixed and heated with mechanical stirring until the reaction became exothermic. The temperature was then maintained at 90° to 100° C. for thirty minutes or until the mixture became too stiff to stir. One hundred twenty-five grams of cold water were then added, and the mixture was heated with stirring at 100° C. until the clear solution formed reached the calculated ionizable chloride content (3.9 per cent Cl₁ for a 44 per cent solution indicating 100 per cent reaction). Twenty-six grams of water were then distilled off to remove unreacted organic material and to give a clear, pale yellow 50 per cent solution containing 4.4 per cent chloride.

The compound thus prepared was tested by determining the time required for a given concentration to kill 99.99999 per cent of the number of microorganisms present in a strain of *Escherichia coli*. A concentration of seventy-eight parts per million was required to obtain this result after thirty seconds, whereas a concentration of 195 parts per million of a commercial

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sample of (lauryl, dimethyl, benzyl) ammonium chloride was necessary to achieve the same results in sixty seconds.

The other compounds are prepared in the same manner using the appropriately substituted benzyl chloride and alkyl dimethyl amine. Readily available mixtures of isomeric benzyl halides in which the benzene ring has its alkyl substituents distributed in the positions that they take when the corresponding alkyl benzene is chloromethylated, are suitable for use in making compounds of the present invention.

When the specific 2-, 3-, or 4-ethyl benzyl chlorides are separately used as starting materials in place of the isomeric mixture, the final quaternary ammonium compounds are not visibly distinguishable from the product of the above example. The other compounds listed above can also be correspondingly prepared from specific isomers if desired and without any significant differences in properties aside from some variations in antimicrobial effectiveness.

The substitution of the chlorine on the benzene ring is sufficiently effective to raise the activity of the Ar-monomethyl benzyl compound to the point that the resulting compound is quite valuable. The monochloro monomethyl compound, for example, is very inexpensively prepared in the above manner from chloro-methylated chlorotoluene and lauryl or n-dodecyl dimethyl amine.

When purified dodecyl compounds are used in place of the natural lauryl mixture, the quaternary products show about the same or slightly higher activity. Apparently the presence of a 14-carbon alkyl chain in the quaternary compounds of the invention does not contribute any significant increase in activity.

The activity of the above compounds appears to be associated exclusively with the cation portion of the molecule. These cations show substantially the same activity whether combined in the form of chlorides, bromides, other halides, or the other anions of the above-listed acids. The free hydroxides are relatively strong bases readily prepared by reacting the corresponding halides with silver oxide, or the corresponding sulphate with an aqueous solution of barium hydroxide. The free base can be neutralized with any acid to form the desired antimicrobial compounds as listed above.

It is extremely difficult to isolate the prepared compounds in pure form inasmuch as they are usually deliquescent and rapidly absorb water from the atmosphere and even from mixtures with absolute (over 96 per cent) ethanol. In high concentrations, that is, with only a small water content, the compounds of the invention do not lose water to anhydrous calcium chloride in a vacuum desiccator. The boiling down of concentrated aqueous solutions of these materials is not feasible by reason of the fact that even heating is impossible and the solutions tend to bump or suddenly liberate vapors with considerable violence, usually causing liquid to be shot out with the vapors. The quaternizing reactions do not go to completion in the absence of solvent because of mechanical difficulties.

High concentrations (90 per cent or over) of the new quaternary compounds can be prepared by carrying out the quaternizing in relatively volatile solvents such as absolute alcohol or acetone and then evaporating off the solvent. Such 90 per cent preparations are clear, pale yellow, extremely viscous syrups, which tend to form skins on their surface upon standing in a desiccator. The syrups are extremely soluble in water, ethanol, isopropanol, acetone, benzene, ethyl ether, and ethyl acetate although practically insoluble in petroleum ether. With dilute aqueous solutions of sodium picrate they react to form water-insoluble yellow oils.

The 90 per cent by weight (Ar-ethyl-benzyl, lauryl, dimethyl) ammonium chloride (the balance being essentially water) has a specific gravity of 0.936 at 30° C. with respect to water at the same temperature. Its index of refraction for the yellow sodium lines at 25° C. is 1.495. The syrups of the other compounds have corresponding values.

The new compounds can be prepared in dry form on a suitable carrier such as urea to yield free-flowing powders containing at least 20 per cent of the quaternary compound by weight.

By reason of the cationic surface activity of the quaternary compounds of the invention, they are also highly effective as wetting, dispersing, or froth flotation agents. They may be utilized as textile finishing agents to impart softness, for example, to the treated goods. Applied to woolen fabrics they also exhibit valuable moth-proofing characteristics. They are not irritating to the skin or body nor toxic in use dilutions.

The characteristics of the new compounds include strong algicidal and fungicidal behavior as well as effective action as deodorants.

The compounds of the present invention all show much higher bactericidal activities than the corresponding (benzyl, lauryl, dimethyl) compounds in which the benzene ring is not alkylated. This is indicated by the following comparison of phenol coefficients, all determined at 20° C. by the standard method given in the U. S. Department of Agriculture Circular 198:

	<i>Staphylococcus aureus</i>	<i>Salmonella typhosa</i>
35 1. (Benzyl, n-dodecyl, dimethyl) ammonium chloride	416	312
2. (Ar-ethyl-benzyl lauryl dimethyl) ammonium chloride	766	600
3. (Ar-dimethyl-benzyl, lauryl, dimethyl) ammonium chloride (isomeric mixture of dimethyl benzyls)	500	625
40 4. (2,4-dimethyl-benzyl, lauryl, dimethyl) ammonium chloride	666	500
5. (3,4-dimethyl-benzyl, lauryl, dimethyl) ammonium chloride	750	500
45 6. (Ar-n-butyl benzyl, n-dodecyl, dimethyl) ammonium chloride	1,000	560

The other compounds of the present invention are of comparable or even higher activity.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope hereof, it is to be understood that the invention is not limited to the specific embodiments hereof except as defined in the appended claims.

What is claimed is:

1. A quaternary ammonium compound selected from the class consisting of the free base and the salts with non-toxic water-soluble acids of (Ar-alkylated benzyl, lauryl, dimethyl) ammonium hydroxide in which the benzene ring is alkylated with at least one alkyl group and with a total number of from 2 to 4 carbon atoms.
2. An (Ar-butyl benzyl, lauryl, dimethyl) ammonium halide.
3. An (Ar-dimethyl benzyl, lauryl, dimethyl) ammonium halide.

References Cited in the file of this patent

UNITED STATES PATENTS

2,676,986 Wakeman et al. ----- Apr. 27, 1954