Patented June 24, 1941 2,246,524

UNITED STATES PATENT OFFICE

2,246,524

GERMICIDE

Lucas P. Kyrides, Webster Groves, Mo., assignor to Monsanto Chemical Company, St. Louis, Mo., a corporation of Delaware

No Drawing. Application August 10, 1938, Serial No. 224,116

11 Claims. (Cl. 167—22)

The present invention relates to agents for the control of micro-organisms, that is, germicides, antiseptics, bactericides, etc., and to compositions containing such agents. The invention relates particularly to a class of N-alkylated alkylene polyamines and their salts which have been found to be eminently suitable for such purposes.

It is among the objects of the present invention to provide a water-soluble active agent for the control of micro-organisms which agent shall have uniformly high germicidal power toward a wide range of micro-organisms. Another object of the invention is to provide a germicide whose activity is not appreciably affected by serum. An additional object is to provide a method of formulating compositions comprising these germicides to obtain most favorably these objects. Other objects and advantages of the invention will be apparent from the description which follows hereinafter. As used throughout this specification the term "germicide" is to be understood to have a broad significance and to include such terms as antiseptics, bactericides, disinfectants, preservatives, etc., which are commonly employed to designate agents for the control of bacteria.

A wide variety of germicides are in common use today. These materials can for the most part be classified into three groups, viz., phenols and substituted phenols, halogens and halogen-engendering compounds, and mercury and heavy metal compounds. The germicides of the present invention belong to none of these groups, and lack many of the objectionable characteristics of each of the groups. The phenolic germicides in general have a destructive or caustic action on tissue which makes it impossible to keep them in contact with tissue at any great concentration for long periods of time. Furthermore, phenols in general have a low solubility in water. Because of their low solubility in water, phenols are used in emulsified form with soaps or the like, for example, in disinfectants of the "lysol" type. The halogens, of which iodine, chlorine, and compounds which liberate chlorine are the outstanding examples, also have a caustic action on tissue and are odorous and fugitive. Iodine is not water-soluble and solvents such as alcohol or aqueous potassium iodide solutions must be used to prepare compositions of germicidal effectiveness. The mercury and heavy metal compounds are, in general, expensive, and although they have a high specificity toward particular organisms they have only a limited range of usefulness in controlling certain other specific organisms. Furthermore, mercurial germicides often exhibit bacteriostatic action, that is, they prevent growth of micro-organisms but do not destroy them completely. In the presence of serum many germicidal materials, especially oxidizing agents, are rendered ineffective.

I have now discovered that certain N-alkylated alkylene polyamines and their salts with acids are remarkably effective germicides which are characterized by a wide range of usefulness for a wide variety of micro-organisms. These N-alkylated alkylene polyamines are substantially free from objectionable odor and have no substantial corrosive or caustic action on tissue when used in dilute solution. Many of the products are soluble in water and such solutions have exceptionally low surface tensions. In the presence of serum, these germicidal materials exhibit a loss of germicidal power but this reduction of effectiveness is only of the order of 50%. These N-alkylated alkylene polyamines are non-staining and have detergent properties which together with their lack of caustic action on tissue make them eminently suitable for washing textiles, rubber goods, walls and floors and especially for washing hands and skin.

The compounds for use according to the present invention consist of N-alkylated alkylene polyamines and their salts with acids. Dodecyl diethylene triamine,

$$C_{12}H_{25}—NH—C_2H_4—NH—C_2H_4—NH_2$$

and hexadecyl triethylene tetramine,

$$C_{16}H_{33}—NH—C_2H_4—NH—C_2H_4—NH—C_2H_4—NH_2$$

are typical compounds for use in the invention. In general, the compounds which are suitable are alkylene polyamines substituted in one or more of the amino groups by one or more alkyl groups containing 8 or more carbon atoms and salts of these amines with acids. Best effects are obtained, however, when the alkylene polyamine contains only one long-chain substituent in one amino nitrogen atom, and the amino nitrogen atom in which the alkyl group is substituted is a

terminal nitrogen atom. The most active agents of the class are those containing from 8 to 18 carbon atoms, inclusive, in the alkyl group. The alkylene polyamines which are suitable for alkylation to obtain useful agents according to the invention are those having not more than 6 nitrogen atoms per molecule which may be obtained by the reaction of ammonia with dihalogenated ethane or propane having the halogens on different carbon atoms, that is, having not more than one halogen on any single carbon atom. Such alkylene polyamines include ethylene diamine and propylene diamine, diethylene triamine, triethylene tetramines, dipropylene triamines, and the like. Only those polyalkylene polyamines having not more than one amino group attached to any single carbon atom are preferred. Such alkylene polyamines may also be obtained by other known methods of synthesis. Furthermore, the compounds may be more complex than those represented, for example, they may be a complex amine such as

$$NH_2CH_2CH_2NHCH_2CH_2CH_2NHCH_2CH_2NH_2$$

resulting from reaction of an excess of ethylene diamine with trimethylene dichloride, or they may be condensation products of alkylene polyamines with each other or with further quantities of alkyl dihalides. The formulae of suitable alkylene polyamines which may be alkylated to obtain desirable agents for use according to the invention are exemplified by:

Ethylene diamine	$NH_2—CH_2CH_2—NH_2$
Trimethylene diamine.	$NH_2—CH_2CH_2CH_2—NH_2$
Propylene diamine	$NH_2—CH_2—CH(NH_2)—CH_3$
Diethylene triamine.	$NH_2—CH_2CH_2—NH—CH_2CH_2—NH_2$
Dipropylene triamines.	$NH_2—CH_2CH_2CH_2—NH—CH_2CH_2CH_2—NH_2$ $CH_3—CH(—NH_2)—CH_2—NH—CH_2—CH(NH_2)—CH_3$ $CH_3—CH(NH_2)—CH_2—NH—CH_2CH_2CH_2—NH_2$

Since the nomenclature of the alkylene polyamines having more than two nitrogen atoms is rather complex, I have, as in the above list, grouped together all the various isomeric compounds as dipropylene triamines, tripropylene tetramines, etc. and refer to them throughout this specification in that manner.

It is not essential in order to obtain effective germicidal action that the alkylated alkylene polyamine base be soluble in water, however, since the compounds may be used in the form of emulsions. Either the free amine or its salts with acids may be used. The salts are in general more soluble than the free amines. The compound N,N'-didodecyl ethylene diamine is not soluble in water to the extent of 1 part in 20,000 parts of water. However, N,N'-didodecyl ethylamine diamine that is emulsified in water containing 10% alcohol gives a composition of effective germicidal strength as is indicated in the results which are given in the table hereinafter.

Representative preferred compounds for use within the purview of this invention are as follows:

Ethylene diamine or propylene diamine derivatives in which one of the nitrogen atoms of the diamine have been substituted by an octyl radical. Diethylene triamine and dipropylene triamine derivatives in which one of the nitrogen atoms of the triamine has been substituted by a decyl, undecyl, dodecyl, tridecyl or tetradecyl radical. Triethylene tetramine or tripropylene tetramine derivatives in which one of the nitrogen atoms of the tetramine has been substituted by a decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl or octadecyl radical. As used herein, the term "nitrogen atom substituted by an alkyl group" is to be understood to mean that one of the hydrogens attached to the nitrogen atom is replaced by an alkyl group, according to the common use of the term "substitution" as applied to aromatic or acyclic compounds.

The compounds which are suitable for use according to the present invention are thus N-alkylated alkylene polyamines consisting of alkylene polyamines having more than 2 and not more than about 6 amino groups per molecule, the different amino groups of which are separated from one another by an alkylene radical selected from the group consisting of ethylene, propylene and trimethylene radicals, at least one of the amino nitrogen groups of which is substituted by an alkyl group having at least 8 carbon atoms.

Examples of specific compounds whose use is contemplated herein are N-octyl ethylene diamine, N-2-ethylhexyl ethylene diamine, N-decyl ethylene diamine, N-tetradecyl ethylene diamine, N,N'-didodecyl ethylene diamine, N-dodecyl diethylene triamine, N-tetradecyl diethylene triamine, N-hexadecyl triethylene tetramine, N-octyl trimethylene diamine, etc. Mixtures of such compounds consisting either of compounds derived from the same alkylene polyamine with different alkyl substituents, such as would result on treating ethylene diamine with mixed alkyl dichlorides, or mixtures of varying degrees of alkylation or mixtures containing compounds derived from different alkylene polyamines with the same or different or mixed alkyl substituents are also contemplated for use herein. A preferred mixture consists of that resulting from alkylation of ethylene diamine, diethylene triamine, or triethylene triamine with alkyl halides having from 10 to 14 carbon atoms, which may be obtained by reacting with thionyl chloride the alcohol fraction resulting from the hydrogenation of cocoanut fatty acids.

Various methods of preparing compounds suitable for use acccording to this invention are known. A preferred method of preparing the compounds consists in alkylating the alkylene polyamines by means of an alkyl chloride. Long-chain alkyl chlorides may be obtained by treating long-chain alcohols with an agent such as thionyl chloride. Lauryl (dodecyl) chloride, for example, can be obtained by treating with thionyl chloride the lauryl alcohol fraction derived from the hydrogenation of cocoanut fatty acids. Mixtures of alcohols containing alcohols having from 10 to 16 carbon atoms consisting predominantly of even-numbered carbon-atom alcohols may be used for obtaining corresponding mixed alkyl chlorides and alkylated alkylene polyamines. These mixed alkylated alkylene polyamines are for some purposes as suitable for use in the invention as the compounds derived from a single isomer or homologue.

The alkyl chlorides can be made by other methods, for example, by means of the reaction of alcohols with dry hydrogen chloride using zinc chloride as a catalyst.

The alkylene polyamine is alkylated by heating with the alkyl chloride even without pressure; superatmospheric pressure and elevated temperatures may be used advantageously.

The extent to which alkylation is conducted determines the relative amounts of mono- and

poly-alkyl substitution. The mono- alkyl alkylene polyamine may be obtained in pure form by fractional distillation.

An example of a method of preparing a typical compound of the invention, N-n-hexadecyl triethylene tetramine,

$NH_2—C_2H_4—NH—C_2H_4—NH—C_2H_4—NH—C_{16}H_{33}$

follows: A fraction of alkyl chlorides (boiling at 150° to 160° C. at a pressure of 2 to 3 mm.) obtained by reaction with thionyl chloride of the fraction of fatty alcohols derived from hydrogenation of cocoanut fatty acids having a boiling point of 180° to 185° C. at a pressure of 15 mm. was used. This fraction of the alcohols corresponded approximately to hexadecyl alcohol and the alkyl chloride formed was substantially pure n-hexadecyl chloride. One mol of this hexadecyl chloride was heated at about 150° C. with about five mols of triethylene tetramine for about 5 hours. The reaction mixture, on cooling, separates into two layers. The upper layer contains the desired reaction product and is distilled under vacuum to separate the unreacted triethylene tetramine. The resulting hexadecyl triethylene tetramine was purified by distillation under vacuum. Its boiling point is approximately 230° to 250° C. at a pressure of 2 to 3 mm. and is a viscous oil which dissolves in water with a most persistent foam.

In a similar manner other N-alkylated alkylene polyamines may be prepared from corresponding alkylene polyamines and alkyl chlorides. The boiling points of several of these substantially pure N-alkylated alkylene polyamines prepared in this manner are as follows:

	Boiling point, millimeters
N-n-octyl ethylene diamine	118°–121° C./10
N-2-ethylhexyl ethylene diamine	108°–110° C./12
N-n-decyl ethylene diamine	140°–145° C./ 9
N-n-tetradecyl ethylene diamine	187°–191° C./ 9
N,N'-di-(n-butyl) ethylene diamine	110°–115° C./15
N-n-dodecyl diethylene triamine	204°–206° C./ 8
N-n-tetradecyl diethylene triamine	190°–197° C./ 2

The effectiveness of the germicides of this invention is shown by the phenol coefficients of various members of the series that are tabulated hereinbelow. The phenol coefficients of several other compounds are also given for comparison. These phenol coefficients were determined at 20° C. by the method of the U. S. Food and Drug Administration against two standard organisms, *Eberthella typhi* and *Staphylococcus aureus*. The phenol coefficients vary somewhat with the acidity or alkalinity of the solution and the results with several of the compounds are shown at various pH values to illustrate this variation. In the results, unless otherwise indicated, alkylated alkylene polyamine was added to water to make a 0.1% solution (1 gram per liter of water) and sufficient hydrochloric acid was added to make a clear solution and to attain the desired pH value. These solutions were subsequently diluted and used for the tests. The pH did not change substantially on dilution but changes of pH did occur when the solutions were added to the different culture media. The polyamines were present as hydrochlorides in the solution except in those cases which are indicated where- in the free base was used or the acetic acid salt was used instead of the hydrochloric acid salt. The phenol coefficients were as follows:

	Phenol coefficient at 20° C. against—		
	pH of 0.1% solution	*Eberthella typhi*	*Staphylococcus aureus*
Ethylene diamine (free base)	----------	<1.1	<1.6
Diethylene triamine (free base)	----------	<1.1	<1.6
N-n-octyl ethylene diamine hydrochloride	7.9	4.4	1.6
N-n-dodecyl ethylene diamine hydrochloride	6.9	133	45
N-n-tetradecyl ethylene diamine hydrochloride	7.4	111	66.6
	6.0	166	----------
	4.7	133	----------
N-n-hexadecyl ethylene diamine hydrochloride	*7.0	166	50
N-n-octadecyl ethylene diamine diacetate	*4.4	<77	<66
N-n-dodecyl diethylene triamine base	9.7	100	50
N-n-dodecyl diethylene triamine hydrochloride	8.5	82	50
	8.0	----------	39–66
	6.5	78	<40
	5.5	44	<16
N-n-tetradecyl diethylene triamine hydrochloride	4.9	78	17
N-n-hexadecyl triethylene tetramine hydrochloride	6.0	67	60
N,N'-n-dibutyl ethylene diamine (free base)	----------	1.1–4.4	Below 1.6
N,N'-n-didodecyl ethylene diamine (emulsified in 10% alcohol 90% water)	----------	60–90	16–20
N-n-decanoyl ethylene diamine hydrochloride	2.3	72	1.6

*pH of a 1.0% solution.

The magnitude of the changes in pH value which occur on adding solutions of the germicides to the culture medium are shown in the following results: Two 0.1% solutions were made of n-dodecyl diethylene triamine and their pH values were adjusted to 5.65 and 8.5, respectively, with hydrochloric acid. These solutions were added to the *Staphylococcus aureus* culture media and the pH values were found to be 6.8 instead of 5.65 and 8.3 instead of 8.5. The acidity of the *Staphylococcus* culture medium itself was 7.9, to which fact can no doubt be attributed these changes in acidity. The phenol coefficients of the solutions as determined at 20° C. by the F. D. A. method for the two solutions were as follows:

	Phenol coefficient at 20° C.		
	pH of 0.1% solution	*Eberthella typhi*	*Staphylococcus aureus*
N-n-dodecyl diethylene triamine hydrochloride	5.65	44	16
	8.5	77	50

Inasmuch as there is a difference in the phenol coefficient of solutions of the germicides of the invention of different acidities and the optimum phenol coefficients are found at approximately the neutral point, it is preferred in preparing germicidal solutions according to the present invention to adjust the acidity to a value at or about a pH of 7. As can be understood, solutions having an acidity greater or less than this can be used but, in either case, correspondingly larger proportions of the alkiated alkylene polyamine constituent will be required to attain the same phenol coefficient.

Substantially neutral or slightly alkaline dilute solutions of the alkylated alkylene polyamines have substantially no irritating effect on the skin or mucous membranes. They are somewhat

astringent in action, however, and have a bitter taste and a soapy feel.

Instead of using the free bases or their hydrochlorides or acetates, other salts, for instance, nitrates, sulfates, alkyl sulfates, phosphates, or salts with organic acids, for instance, formates, lactates, tartrates, citrates, benzene or toluene sulfonates, benzoates, salicylates, etc. may be employed. Preferably those water-soluble alkylated alkylene polyamines in which the alkyl radical contains 8 to 18 carbon atoms or mixtures of these are used because of their water solubility.

Although I prefer to use my germicidal materials in aqueous solutions, compositions may be prepared by the use of a wide variety of other solvents. The alkylated alkylene polyamines are soluble in alcohols such as ethyl alcohol and isoamyl alcohol; hydrocarbons such as benzene, xylene, mineral oil, and kerosene; vegetable and animal oils such as cottonseed oil and linseed oil; and in chlorinated hydrocarbons such as carbon tetrachloride. This solubility is suggestive of a wide variety of germicidal compositions which may be prepared with the compounds.

The alkylated alkylene polyamines have proved suitable for the most various preserving and disinfecting purposes. For example, they may be employed for the disinfection of all kinds of table utensils, surgical instruments, etc. They are further advantageously used for disinfecting purposes in medical practice, for instance, for articles used in dressing wounds, for rubber goods, for disinfecting laundry and for the scrubbing of hands; furthermore, for cosmetics, for instance, face powder, hand lotions and media for hyperidrosis. Floors and walls may likewise be disinfected. Dilute solutions may be used for irrigation of body cavities, bladder lavages, urethral irrigations and vaginal douches. Foodstuffs such as fruits, vegetables, meat, etc. may be preserved or disinfected by these germicides, which are easily washed therefrom. They are also further suitable for preservation of animal materials such as skins, blood, glands and other organs, etc. In some instances a germicidal composition which leaves a stain to indicate its presence on tissue, etc. is desirable and this result may be obtained by tinting solutions of the alkylated alkylene polyamines by means of known dyestuffs.

My new disinfecting media may be diluted with hard water without diminution of their activity or precipitation of insoluble salts. Solutions of the compounds in water have a penetrating action as a result of their low surface tension. Water at 25° C. has a surface tension of about 72.8 dynes per centimeter. Solutions of the alkylated alkylene polyamines in the table hereinbelow have the surface tensions at the concentrations indicated at 25° C.

	Surface tension of solutions at 25° C.			
	0.125%	0.03125%	0.0078%	0.0039%
Dodecyl diethylene triamine	30.3			
n-Hexadecyl triethylene tetramine	33.7	34.0	36.6	
Decyl-tetradecyl diethylene triamine	31.0	31.3	30.7	38.2

In formulating germicidal solutions, penetrants which reduce the surface tension of the solution are frequently incorporated. With the germicides of the present invention these additional constituents are rendered unnecessary since the germicide acts as its own penetrating agent.

Inasmuch as the above specification comprises preferred embodiments of the invention it is to be understood that the invention is not limited thereto and that changes and modifications may be made therein without departing substantially from the invention which is defined in the appended claims.

I claim:

1. An agent for the control of bacteria, which comprises a compound selected from the group consisting of N-alkylated alkylene polyamines and salts thereof with acids, said N-alkylated alkylene polyamines corresponding to the general formula

$$X—NH—R—(NH—R)_n—NH—Y$$

in which R is an alkylene radical selected from the group consisting of ethylene, propylene and trimethylene radicals, n is a number from 0 to 4, and X and Y are selected from the group consisting of hydrogen and alkyl radicals at least one of which is an alkyl radical having not less than 12 and not more than 16 carbon atoms.

2. An agent for the control of bacteria, which comprises a compound selected from the group consisting of alkylene polyamines and salts thereof with acids, said alkylene polyamines having more than 2 and less than 6 amino radicals per molecule, the different amino radicals of which are separated from one another by an alkylene radical selected from the group consisting of ethylene, propylene and trimethylene radicals, at least one of the amino radicals of said alkylene polyamine being substituted by an alkyl radical having not less than 12 and not more than 16 carbon atoms.

3. An agent for the control of bacteria which comprises a compound selected from the group consisting of alkylated diethylene triamines and salts thereof with acids in which the alkylation has been effected at a terminal nitrogen atom with an alkyl radical containing not less than 12 and not more than 16 carbon atoms, said agent being characterized by an improved resistance to loss of activity in the presence of organic matter.

4. An agent for the control of bacteria which comprises a compound selected from the group consisting of N-dodecyl diethylene triamine and salts thereof with acids, in which the dodecyl radical is attached to a terminal nitrogen atom.

5. An agent for the control of bacteria which comprises a compound selected from the group consisting of N-tetradecyl diethylene triamine and salts thereof with acids, in which the tetradecyl radical is attached to a terminal nitrogen atom.

6. An agent for the control of bacteria which comprises a compound selected from the group consisting of N-hexadecyl triethylene tetramine and salts thereof with acids, in which the heaxadecyl radical is attached to a terminal nitrogen atom.

7. The method of suppressing the growth of bacteria on a material which comprises applying to the material an agent as defined in claim 1.

8. The method of suppressing the growth of bacteria on a material which comprises applying to the material an agent as defined in claim 2.

9. An agent for the control of bacteria which comprises N-dodecyl diethylene triamine, in

which the dodecyl radical is attached to a terminal nitrogen atom.

10. An agent for the control of bacteria which comprises N-tetradecyl diethylene triamine, in which the tetradecyl radical is attached to a terminal nitrogen atom.

11. An agent for the control of bacteria which comprises N-hexadecyl triethylene tetramine, in which the hexadecyl radical is attached to a terminal nitrogen atom.

LUCAS P. KYRIDES.

CERTIFICATE OF CORRECTION.

Patent No. 2,246,524. June 24, 1941.

LUCAS P. KYRIDES.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows: Page 2, first column, line 58, for "ethylamine" read --ethylene--; page 4, second column, line 63-64, claim 6, for "heaxadecyl" read --hexadecyl--; and that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 5th day of August, A. D. 1941.

Henry Van Arsdale,
Acting Commissioner of Patents.

(Seal)