

PATENT SPECIFICATION

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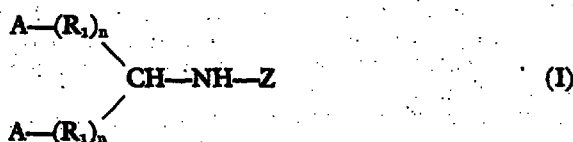
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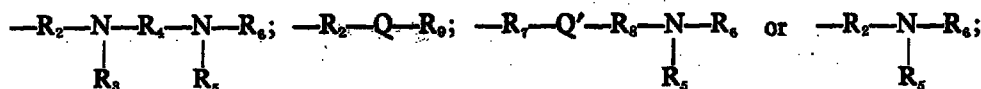
(54) ALKYL POLYAMINES HAVING A CYCLIC SUBSTITUENT, METHODS OF PREPARING SUCH COMPOUNDS, AND THEIR USE AS ANTIMICROBIALS

(71) We, MERCK & CO. INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention provides a new class of substituted polyamines having the structural formula:



where each A, independently of the other, is a cyclohexyl, (C₁₋₆ alkyl)-substituted cyclohexyl, cyclohexenyl or (C₁₋₆ alkyl)-substituted cyclohexenyl radical; each n, independently of the other, is 0 or 1, each R₁, independently of the other, is C₁₋₄ alkylene, e.g. methylene, ethylene or trimethylene, and Z is a radical of formula



where Q is 1,4-piperidinediyl or 1,4-piperazinediyl; Q' is 1,4-cyclohexylene; each of R₂ and R₄ is 2-hydroxy-1,3-trimethylene or C₁₋₄ alkylene; R₃ is hydrogen, C₁₋₄ alkyl, C₂₋₄ aminoalkyl, C₁₋₄ hydroxyalkyl or C₂₋₄ dihydroxyalkyl, e.g., 2,3-dihydroxypropyl or 3,4-dihydroxybutyl; R₅ is hydrogen, aminoethyl, aminopropyl, C₁₋₄ monohydroxyalkyl, or C₂₋₄ dihydroxyalkyl; R₆ is hydrogen, C₁₋₄ monohydroxyalkyl or C₂₋₄ dihydroxyalkyl; R₇ is 2-hydroxy-1,3-trimethylene, C₁₋₄ alkylene or a chemical bond between the cyclohexylene residue and a first nitrogen; R₈ is 2-hydroxy-1,3-trimethylene, C₁₋₄ alkylene or a chemical bond between the cyclohexylene residue and a second nitrogen and R₉ is aminoethyl, aminopropyl, or aminohydroxypropyl. Preferably R₃, R₅ and R₆ are not simultaneously dihydroxyalkyl, but when they are it is preferred that they be C₂ or C₄ dihydroxyalkyl.

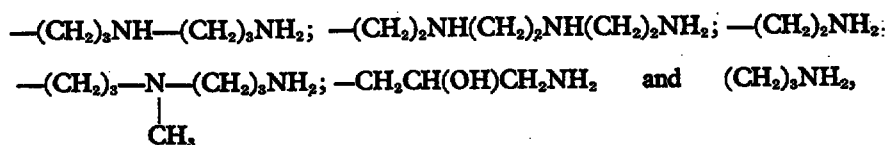
Preferred polyamines I are those in which the sum of the carbon atoms in both of R₁ is from 2 to 8.

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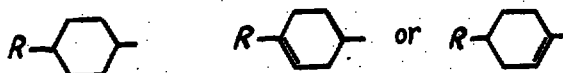
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Among suitable values of Z are



and a particularly preferred group of compounds are those in which Z has one of these values; n is 1, R₁ is methylene, ethylene, trimethylene, or tetramethylene and each A is



where R is hydrogen, methyl or isopropyl, and their salts. Examples of such compounds are 1-(1,5-dicyclohexyl-3-pentyl)-3-hydroxy-1,5-diazapentane and salts thereof, e.g. the dihydrochloride and dipropionate salts, and N-(1,5-dicyclohexyl-3-pentyl)-ethylenediamine and its dihydrochloride salt.

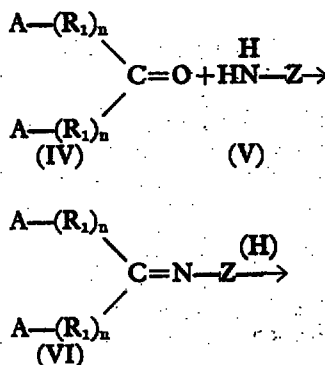
Compounds of this invention have been found to possess broad-spectrum anti-bacterial, antifungal, and anti-algal properties. Especially useful is their activity against bacteria and fungi responsible for stunting the growth and even destruction of many types of crop-producing plants. Thus, compounds of the present invention can be used to protect plants against diseases such as leaf, stem, and fruit spotting, internal discoloration and decay of fruits and vegetables. They can be applied on foliage and trees to control bacterial and fungal diseases. Compounds of the present invention are particularly active against diseases caused by the genera *Pseudomonas*, *Xanthomonas*, *Erwinia*, and *Corynebacterium*.

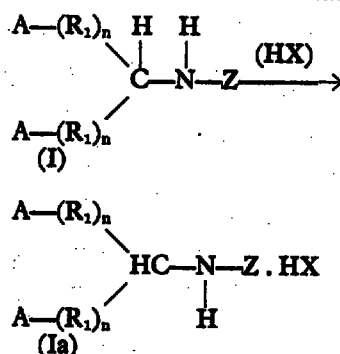
In agriculture, a severe problem faced in the raising of cotton beans, corn and other crops is the loss of yield per acre due to the action of soilborne fungi on seed and on the roots of the young plants. Control or elimination of these losses can be accomplished by the use of compounds of the present invention as soil disinfectants.

Compounds of the present invention are especially useful as an agent active against bacterial disease of fruits such as fireblight. Streptomycin, which is the prime agent currently useful, is not only expensive but being an antibiotic useful in human medicine, is regarded by some as a source in agricultural use of streptomycin-resistant species of pathogens.

Compounds of the present invention are also active against bacteria and fungi that cause the degradation and deterioration of many types of materials, including papers, leather, textiles, aqueous preparations such as latex paints, adhesives, resins, pigment dispersions and oleoresinous coatings whose films are particularly vulnerable to the destructive action of fungi. The large economic losses encountered in paper-making operations caused by the accumulation of bacterial and fungal slimes in various parts of the water system can be eliminated to a significant extent by the use of compounds of the present invention.

The compounds of this invention are preferably prepared according to the following sequence of reactions:

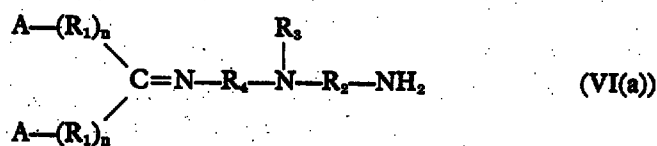




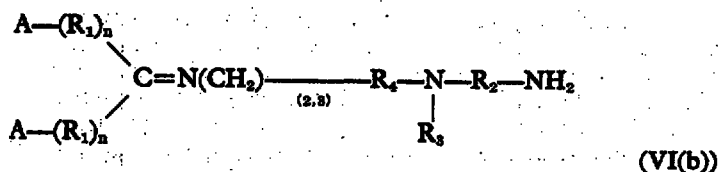
where A, Z and n have their previously defined meanings, HX is a monobasic or polybasic organic or inorganic acid, and sufficient HX is provided to protonate at least one amino group of compound I.

The preparation of polyamine I comprises the straightforward Schiff base reaction of the appropriate ketone IV and the appropriate amine V.

If amine V has two primary amino groups, it can either be symmetrical or unsymmetrical. An amine V, which is a symmetrical amine, e.g., where R_2 and R_4 are alike when R_5 and R_6 are hydrogen; or where R_2 and R_4 are ethylene, R_5 is aminomethyl, and R_6 is hydrogen; or where R_2 is trimethylene when R_5 is 3-aminopropyl and R_6 is hydrogen; forms a single Schiff base VI. This is because regardless of which terminal primary amino group of amine V reacts with ketone IV, the same product results. However, where amine V is unsymmetrical two products can result. One is Schiff base VI. The other products have the formula VI(a) when R_5 and R_6 are hydrogen:



or VI(b) when R₅ is aminoethyl or aminopropyl:



where A, R_{1-n}, and n are as previously defined. Note that both products VI(a) and VI(b) come within the scope of the definition given for Schiff base VI. Where Schiff bases of formulas VI and VI(a) or VI(b) are produced they can be separated, if desired, by the usual and well known separation techniques, e.g., distillation.

As an alternative to obtaining a mixture of Schiff bases VI and VI(a) or VI(b), the reaction can be conducted stepwise. For example, 1,2-diaminoethane may be converted to a Schiff base with 1,5-di-(4-isopropylcyclohexyl)-3-pentanone and catalytically reduced, the ring nitrogen then being selectively cyanoethylated with acrylonitrile, followed by catalytic hydrogenation to furnish [1,5-di-(4-isopropylcyclohexyl)-3-pentyl]-1,4,8-triazaoctane.

To prepare Schiff base VI, ketone IV and amine V are dissolved in a suitable inert solvent, for example, toluene, and heated to reflux, until reaction is substantially complete. Usually 5 to 20 hours is sufficient for water removal by azeotropic distillation. The solvent is then removed under reduced pressure and the residue comprising the Schiff base VI is dissolved in an inert solvent, preferably an alkanol, such as ethanol or isopropanol.

After dissolution, the Schiff base VI is catalytically or chemically reduced.

If reduction is catalytic, any unsaturated carbon to carbon bond in A will also be reduced or hydrogenated, as well as the carbon to nitrogen bond of the Schiff base VI. In such catalytic reductions, hydrogen saturates an alkanol solution of Schiff base VI using agitation in the presence of the usual hydrogenation catalysts, such as

transition metals and their reducible oxides. Especially effective catalysts are the noble metals and their oxides. A particularly preferred catalyst is platinum oxide. Generally, the hydrogenation reaction is carried out in a well known manner. Small particles, e.g., 100—300 mesh of catalyst are admixed with the Schiff base and excess of amine in alcohol and placed in a closed system pressurized with from 3—5 atmospheres of hydrogen gas, preferably at ambient temperature, and generally at such pressures and a temperature of from 15°C. to 45°C. At higher temperatures the pressure preferably need not exceed 15 atmospheres. After reaction is complete, the pressure is released and the catalyst separated from the reaction mixture by filtration. The filtrate containing the cyclohexyl polyamine I is then further purified by usual techniques. Preferably, whatever solvent may be present is removed under reduced pressure, the residue then dissolved in a water-immiscible solvent and washed with water, followed by a further washing with a saturated aqueous inorganic salt solution. After drying, the solvent is removed by evaporation under reduced pressure giving the cyclohexylpolyamine I usually as an oil. The cyclohexylpolyamine can then be redissolved in loweralkanols, mixtures of loweralkanols and water, diethylether or dioxane and then neutralized with an acid, e.g., hydrogen chloride, or neutralized directly with aqueous acids.

Acid-addition salts are then isolated, if desired, by precipitation, evaporation or other usual techniques.

Suitable anions X for the salt I(a) include anions derived from inorganic acids as well as those of organic acids such for example as halide, e.g., chloride, bromide or iodide or sulfate, nitrate, bisulfate, phosphate, acetate, propionate, maleate, succinate, laurate, palmitate, oleate, stearate, ascorbate, gluconate, citrate, carbonate, bicarbonate, benzoate, salicylate, pantoate, phthalate, furoate, picolinate, dodecylbenzenesulfonate, laurylethersulfonate or nicotinate. Generally, any anion derived from an acid is suitable and satisfactory when the polyamine salt anion X⁻, e.g., chloride is replaced with other anions, by well known anion-exchange techniques.

When preparing cyclohexenylpolyamines, that is the product I where olefinic unsaturation in ring A is retained, a selective chemical rather than a catalytic reduction is used to reduce Schiff base VI to product I.

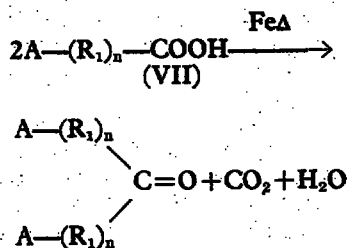
In this chemically reductive procedure, the ketone IV is reacted with the appropriate amine as before, but the Schiff base VI is dissolved in an inert alkanol or ether-type solvent and reacted with a chemical reductant such as sodium borohydride or lithium aluminium hydride, respectively.

Although as little as an equivalent of the chemical reductant can be used successfully, more satisfactory results are obtained if at least a two-molar excess, and preferably at least a 2.5 molar excess, of the chemical reductant is used. After any initial reaction has subsided, the reaction mixture of Schiff base VI and reductant may be heated to reflux for an hour or two, then cooled to room temperature, and afterwards concentrated under vacuum. The residue obtained is then further purified as by treatment with mineral acid or inorganic base as was described for polyamines I and the salt may thereafter be formed as previously described.

The cyclohexyl and cyclohexenyl ketones IV are readily prepared and two alternative methods, are set forth below.

(A) The Condensation of Acids

This method involves the following reaction scheme:



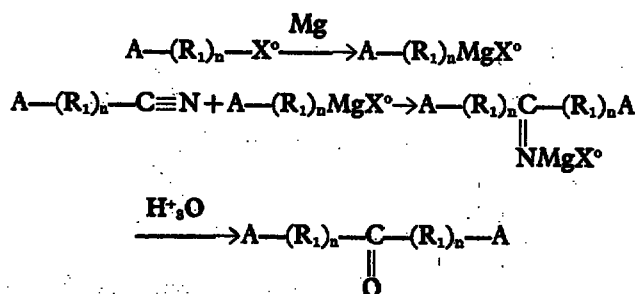
Acylative decarboxylation of acids VII involves heating the acid at elevated temperatures either with transition metals, preferably iron, transition metal oxides, alkaline-earth metal oxides, polyphosphoric acid or boron trifluoride. Most suitably, acylative reaction is achieved by passage of acid vapors over catalysts such as heated thoria aerogel.

Preferably the carboxylic acid VII and iron are agitated under an inert atmosphere of nitrogen for at least 2 hours at 195°C. to 200°C.

The carboxylic acids VII mentioned above are prepared by various well known means. One particularly useful technique is the addition of a cyclohexene to an aliphatic acid anhydride.

Other carboxylic acids are readily obtained, for example, by the Diels-Alder reaction of a diene and alkyl substituted diene with various unsaturated aliphatic compounds or carboxylic acids, as are later referred to in greater detail.

Dicyclohexyl, dicyclohexenyl, or cyclohexyl-cyclohexenyl alkanones can be obtained according to the following reaction scheme:



This general procedure utilizes the reaction of a Grignard reagent prepared from a chloro- or bromo-substituted cyclohexane or cyclohexene derivative with a cyano-substituted cyclohexane or cyclohexene derivative. The resultant disubstituted imino-alkane salt complex is hydrolysed with aqueous mineral acid to the corresponding ketone.

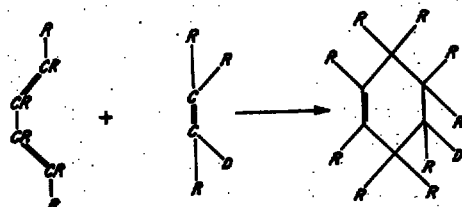
The Grignard reagent is obtained by reaction of the halide with magnesium metal, usually in the form of turnings or powder and may be catalysed by very small concentrations of iodine or methyl iodide. Suitable solvents include diethyl ether, dibutyl ether, tetrahydrofuran, dioxane and benzene. Usually, gentle warming suffices to initiate the reaction and the halide is gradually added to the metal-solvent mixture. After complete addition the disappearance of practically all magnesium metal signifies the end of the reaction. A small excess of halide is used and moisture must be excluded; a nitrogen atmosphere is beneficial. The Grignard reagent is then added to the nitrile which has previously been dissolved in two or three times its volume of solvent over a period of 15 minutes to 1 hour at ambient temperature.

13 14

The reaction mixture may then be heated to reflux to ensure complete reaction. Generally, a small excess of Grignard reagent as compared to nitrile is used. From 1 to 10 hours at reflux is sufficient for complete conversion. The resultant imine salt is preferably decomposed to the ketone with aqueous mineral acids such as hydrochloric, sulfuric and phosphoric acids. The ketones are water-insoluble and may be extracted with water-immiscible solvents. Purification is preferably accomplished by fractional distillation under reduced pressure. It is feasible to use the crude ketone reaction mixture for the alkylation of polyamines as the reaction by-products are usually alcohols or hydrocarbons and do not react with amines. The reactant halides, if present in the crude product, should be removed prior to the ketone-amine alkylation process.

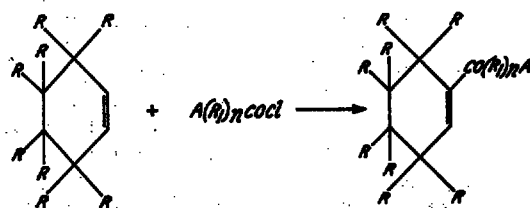
The concentrations of Grignard reagent and nitrile may be varied over wide limits for securing good yields in the process.

The halide and cyano, as well as carboxylic derivatives of cyclohexanes and cyclohexenes are commonly available; where the requisite carboxylic, cyano or halo derivatives as used herein are not readily available they can be obtained by known techniques, for example, by means of the Diels-Alder synthesis:



where D is R, $-(R_1)_n-COOH$, $-(R_1)_n-Br$, or $-(R_1)_n-CN$ and where R_1 , R, and X have their previous meanings. Where D is R and each R is alkyl, the resulting cyclohexene can be reacted with an aliphatic acid anhydride as previously described. Where D is $(R_1)_n-COOH$, $(R_1)_n-CN$ or $(R_1)_n-Br$, the condensation can proceed as outlined in preparative examples A and B above. Of course, $A(R_1)_n-COOH$ can be treated by standard techniques with a phosphorus chloride, e.g., phosphorus pentachloride, to form $A(R_1)_n-COCl$.

Where R is independently either hydrogen or C_1 to C_6 alkyl, the Darzens synthesis [Compt. Rend., 150, 707 (1910)] can be used:



where R_1 , n, R and A are as previously defined. Likewise, the Blaise-Barie synthetic route can be used [Bull. Soc. Chim. [4] 7, 215 (1910) and Compt. Rend. 145, 73 (1907)]:



where A, n and R_1 have their previously defined meanings.

Once the ketone IV is obtained it can then be reacted with a suitable polyamine V. Polyamines V that are exceptionally suitable for reaction with ketone IV include diethylenetriamine, triethylenetetramine, 3,3' - iminobis(propylamine), 3,3' - methyliminobis - (propylamine), dipropylenetriamine, N,N' - bis - (3 - aminopropyl) - 1,3 - trimethylenediamine, N,N' - bis - (2 - aminoethyl) - 1,3 - trimethylenediamine, N,N' - bis - (3 - aminopropyl)piperazine, N - (3 - amino - 2 - hydroxypropyl) - 1,3 - trimethylenediamine, N - (2 - aminoethyl) - 1,3 - trimethylenediamine, spermidine, spermine, 1,4 - bis - (2 - aminoethyl)piperazine, tris - (2 - aminoethyl)amine, 1 - (2 - aminoethyl) - 4 - (3 - aminopropyl)piperazine, 1 - (3 - amino - 2 - hydroxypropyl) - 4 - (2 - aminoethyl)piperazine, N - (3 - amino - 2 - hydroxypropyl) - 1,3 - trimethylenediamine, N,N' - bis - (3 - aminopropyl) - 1,4 - cyclohexylene - bis - (methylamine), 1 - (2,3 - dihydroxypropyl) - 1,5,9 - triazanonane, 1 - (2 - hydroxyethyl) - 1,4,7,10 -

tetraazadecane, 4 - (3,4 - dihydroxybutyl) - 1,4,8 - triazaoctane, 1 - (2 - hydroxypropyl) - 5 - hydroxymethyl - 1,5,9 - triazanonane, 1,4 - di - (3 - aminopropyl) - piperidine, tris - (3 - aminopropyl)amine, ethylenediamine, trimethylenediamine, and 1,3 - diamino - 2 - hydroxypropane.

The compounds described herein are excellent broad spectrum antimicrobial agents which are especially effective against Gram-positive and Gram-negative bacteria, particularly the troublesome Gram-negative of the genus *Pseudomonas* at aqueous concentrations of 1.0 to 100 ppm. Examples of susceptible species include, *inter alia*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bordetella bronchiseptica*, *Pasteurella multocida*, *Escherichia coli*, *Salmonella typhimurium*, *S. pullorum*, *Klebsiella pneumoniae*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Desulfovibrio desulfuricans*, *Bacillus mycoides*, fungi such as *Aspergillus niger* and *Chaetomium globosum*.

For use, these compounds can be applied neat or used in a diluted form. Satisfactory diluents include any inert material not destructive of the antimicrobial activity and especially liquid formulations comprising aqueous dispersions, solutions, and emulsions. Solid diluents include talc, corn starch, alumina and diatomaceous earth. The antimicrobial agents of this invention can also be deposited on materials such as natural fibers including paper, cotton, wool and synthetic fibers such as nylon, polypropylene, as well as upon inanimate surfaces including hard surfaces such as wood, glass, metal, tile, rubber, plastic, and porous surfaces such as concrete and leather.

The polyamines of this invention are especially useful in suppressing the growth of aerobic and anaerobic bacteria in fluids used in cutting and grinding operations, such as metal working, and oil-well drilling muds or secondary oil recovery waters and brines. Anaerobes such as the sulfate-reducer, *Desulfovibrio desulfuricans*, are inhibited at 0.1—10 ppm. concentration of these polyamines. Suppression of these bacteria eliminates hydrogen sulfide production and corrosion of equipment, plugging of oil-bearing sands, malodors and other deleterious actions. These compounds are also useful in the preservation against biodeterioration of other aqueous systems such as aqueous emulsions and dispersions, paints or coatings, pigment suspensions and adhesives where proliferation of microorganisms can produce colloid breakdown, pH shifts, malodors, corrosive substances, viscosity loss and other undesirable effects.

One particularly useful application of the compounds of this invention is imparting sanitizing properties to fabrics, either woven or non-woven, launderable or disposable for use, for example, as diapers, surgical masks, caps, gowns, towels and drapes, covers for hospital furniture and instrument wrappings, aseptic facial tissues, and sanitary napkins and bathroom tissue. In this application, the compound of Formula I can be applied to the fibrous pulp before extracting or strand or thread formation or it can be sprayed upon the finished goods. Either deposition technique is satisfactory so long as 1×10^{-4} % or more by weight of the antimicrobial material is retained on the cloth. More than 1% by weight is generally excessive and superfluous.

Another application is alone or in solution or suspension or in conjunction with soaps or detergents for use in cleansing the skin, particularly in presurgical scrubbing formulations or in formulations for controlling the growth of *Corynebacterium acnes*. *C. acnes* is a strain of bacteria implicated in acne conditions, especially *Acne vulgaris*, wherein applications of as little as 1 to 5 ppm. is effective in controlling such skin-dwelling bacteria. Larger concentrations can be used if desired without irritation or discomfort such as 2500 ppm and higher. Where the cleansing formulation is diluted with water upon use, the formulation can comprise from 0.01% by weight and more of the polyamine of this invention.

In addition, the compounds described herein can be added to impounded water, such as swimming pools, ponds or industrially used water such as cooling or paper-mill water to inhibit growth of undesirable bacteria, fungi, and/or algae.

In the control of slime-producing microorganisms and algae in recirculating industrial waters, particularly cooling operations and especially installations such as cooling towers, the polyamine compounds of this invention are usually used alone, but can also be used in combination with other antimicrobial agents. The compounds are preferably used in the form of salts to enhance solubility. Concentrations in the recirculating water of as little as 1×10^{-4} % by weight are effective in inhibiting microbial growth. To ensure effectiveness, especially against more resistant strains of microorganisms, and also when make-up water is added to replace water lost by evaporation and the like, concentrations of from 1×10^{-4} % to 5×10^{-2} % by weight are most satisfactory. Dosage may be continuous or as intermittent "shock treatment", i.e., addition in a 10—20 minute period every 4—8 hours.

An unusual, highly advantageous property of these compounds is high substantivity to all kinds of surfaces; this provides protection against corrosion and acts

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as a storage depot for continuously dosing the waters in contact. The same properties also are largely responsible for the previously stated utility as disinfectants for inanimate surfaces comprising walls and ceilings, equipment, animal pens, hospital facilities, kitchens and bathrooms.

5 In formulating the compounds of this invention for the above uses, these compounds can be used in combination with other antimicrobial agents, surfactants, insecticides, defoamers, odorants, or as chelates of metals such as copper, calcium, magnesium and iron.

Agricultural Applications

10 Wettable powder formulations for use as a dispersion in water represent a practical means for good distribution in soil. Other methods of achieving the same results include the preparation of dusts. All of the polyamines can be blended as fine powders with the commonly used powder diluents such as talc, clay, refined silicates, wood flour, sand, magnesium oxide, calcium carbonate, fuller's earth, kaolin, diatomaceous earth, mica and pumice. The powder can have the following formula-
15 tion:

Polyamine	Percent
Inert diluent (e.g. clay or talc)	1—75 25—99

20 The mixtures may be finely powdered, e.g., to the 1—10 micron average particle size, or be made by blending the already finely powdered ingredients.

For application as agricultural disinfectants the dusts may be applied to the seed and surrounding soil at the time of planting. The concentration of the sterilant is adjusted to give an effective, nonphytotoxic dosage in the soil. In general, the
25 soil concentration of polyamine should be from 10 to 25 parts per million (of active ingredient). For most economical and effective use the dusts can be applied in bands of 6 to 8 inches centered on the rows just prior to seeding. The material can then be rototilled to a depth of several inches. This mode of treatment saves material and protects the root system of young plants against microbial attack.
30 For the protection of a given crop, such as cabbage, the band spread of antimicrobial can vary from 8 inches for black root disease to 12—15 inches for club root disease prevention. Similarly, the depth to which the fungicide should be distributed can vary from 2 to 6 inches.

The wettable powders can be prepared by the addition of 0.1—5% of a wetting agent to the powder blends. Many dispersing agents are commercially available which are non-phytotoxic at the required concentrations. These may, for example, be alkali metal and amine salts of sulfated and sulfonated acids, alcohols, and oils, or polyethoxylated alkyl phenols, long chain fatty amine quaternary salts, partial fatty acid esters of polyhydric alcohols, etc. Some dispersants can be used in preparing emulsi-
40 fiable concentrates of the polyamines in organic solvents. Many of these agents are available in solvent-soluble form. The manner of application to the soil is similar to the dusts. Spray equipment is used to spread the suspensions or emulsions over the soil and by discing, the fungicidal agents can be uniformly distributed to varying depths. Spray application is also effective for band-limiting the dosages.

45 Other agricultural uses for these formulations involve the eradication of bacterial blights of plants by application to the involved surface areas. Compounds of this invention show high orders of bacterial inhibition and are especially useful for this purpose. Some of the diseases which are of commercial importance in decreasing yield and quality and are controlled by the compositions of the invention are fire blight of apple and pear, bacterial spot on stone fruit, cherry leaf spot, walnut blight,
50 common blight of bean, bacterial spot of tomato and pepper, and potato seed piece decay. The effective concentration of polyamines required varies from 5—200 parts per million; they may be applied as dusts, powder dispersions in water as emulsions in water, or as aqueous dipping baths. Other plant diseases which can be controlled by treatment with these formulations are fungal in origin, such as the many kinds of powdery mildew and leaf scabs.

55 For seed treatment, proportions as low as 1 to 4 ounces per hundred weight (550 to 600 ppm on seed) are effective against various fungi.

60 The compounds of the invention can be used in form of aqueous suspensions or emulsions, the base products being generally insoluble in water. For this type of formulation various powdered carriers can be used to aid in achieving uniform distribution. Talc, fuller's earth, calcium silicate, calcium carbonate, clays and the like are admixed with the agent along with wetting and dispersing agents and sticking agents.

For maximum chemical compatibility those that are non-ionic in character are preferred. Other nonionic or cationic surfactants are also satisfactory.

Additional applications for the compounds of this invention include inhibiting formation of dental plaque especially when used as an oral rinse, e.g., a mouth wash, or in combination with a toothpaste or tooth powder containing from 50—1,000 ppm.

The following specific Examples are further illustrative of the invention. The word "Celite" is a Trade Mark.

Preparation A

Free Radical Addition of Acetic Anhydride to β -Pinene

To 1,000 g. (10 moles) of refluxing acetic anhydride is added dropwise a mixture of 136 g. β -pinene (1.0 mole) and 30 g. *t*-butyl peroxide (0.2 mole) over a period of 2.5 hours. The reaction mixture is then heated at reflux for an additional 5 hours. The acetic anhydride is then removed under vacuum and the residue hydrolysed by treatment with 40 g. NaOH in 250 ml. of water and 150 ml. of ethanol. The mixture is heated at reflux for 2 hours, then acidified with hydrochloric acid, extracted with ether and dried over sodium sulfate. The dried extracts are evaporated to leave a residue which is distilled under vacuum giving 43.1 g. (22%) of 3-(4-isopropylcyclohexenyl)-propionic acid having a b.p. 135°—137°C. (0.3 mm.).

Preparation B

3-(4-Isopropylcyclohexyl)propionic Acid

The unsaturated acid from the previous preparation is dissolved in ethanol and hydrogenated with PtO₂ at room temperature and 40 psi hydrogen pressure. The platinum catalyst is filtered off and the ethanol removed under reduced pressure. The saturated product, 3-(4-isopropylcyclohexyl)propionic acid, is obtained as a colourless liquid: yield 42.3 g. (97%).

Preparation C

Preparation of 1,5-Di-(4-Isopropylcyclohexyl)-3-pentanone

3-(4-Isopropylcyclohexyl)propionic acid (39.7 g., 0.20 mole) and iron (hydrogen reduced, 6.15 g., 0.11 mole) is heated for 1.5 hours at 195°C. under a nitrogen atmosphere. After that time, the temperature is increased to 290°C. and maintained at that temperature for three hours. The cooled reaction mass is extracted well with ether and filtered through Celite, and the ethereal extracts are concentrated under vacuum. The residue is stripped under vacuum to leave the product, 17.3 g. (51%).

Similarly in an analogous manner there are obtained the following ketones.

1,9-Dicyclohexyl-5-nonanone;
1,5-Dicyclohexyl-3-pentanone;
1,3-Dicyclohexylacetone;
1,7-Dicyclohexyl-4-heptanone;
1,3-Di-(3-methylcyclohexyl)acetone;
1,7-Di-(4-ethylcyclohexyl)-4-heptanone;
1,5-Di-(2-isopropylcyclohexyl)-3-pentanone;
1,9-Di-(2-ethylcyclohexyl)-5-nonanone;
1,5-Di-(4-*t*-butylcyclohexyl)-3-pentanone;
1,5-Di-(2,4,6-trimethylcyclohexyl)-3-pentanone;
1,5-Di-(3,5-diethylcyclohexyl)-3-pentanone;
1,7-Di-(2,6-dimethyl-4-*t*-butylcyclohexyl)-4-heptanone; and
1,7-Di-(2,3,4,5,6-pentamethylcyclohexyl)-4-heptanone.

When unsaturated acids are subjected to the above procedure the following representative ketones are obtained:

1,7-Dicyclohex-3-enyl-4-heptanone;
2,8-Di-(4-methylcyclohex-3-enyl)-5-nonanone and
1,5-Di-[4-isopropylcyclohex-1-enyl]-3-pentanone.

Preparation D

Preparation of 4-Cyclohexyl-1-(4-isopropylcyclohexyl)butanone-2

A Grignard reagent was prepared from 2-cyclohexylethyl bromide 21 gm. (0.11 mole) and magnesium, 2.4 g. (0.1 gram atom). The magnesium is covered with 25 ml. of anhydrous ether, a crystal of iodine added and in a nitrogen atmosphere, the halide dissolved in 50 ml. of anhydrous ether is added, once initial reaction is obtained,

at reflux temperature over a period of 1—2 hours. After complete addition, refluxing is continued for 1/2 hour.

In a nitrogen atmosphere, the Grignard solution is clarified by passage through a glass wool filter plug and added slowly to an agitated solution of 4-isopropylcyclohexylacetonitrile, 14.9 gm. (0.09 mole) in 200 ml. of anhydrous diethyl ether. A gentle reflux is maintained during the addition, which requires 1/2 to 1 hour. After complete addition and an additional 15 minutes at reflux, the reaction mixture is cooled and poured onto a mixture of 50 ml. of concentrated hydrochloric acid and 200 gms. of ice using good mixing. Upon warming the ether is removed by distillation and the residue heated at 70°—100°C. for 1 hour. The product is extracted with two 250-ml. portions of ether, the ethereal solution is dried over anhydrous magnesium sulfate and the solvent is removed. Any of the reactants, i.e., halide and nitrile, are separated from the ketone by fractional distillation under reduced pressure along with by-products.

In a similar procedure, the following ketones are prepared:

- 1-(2-Methylcyclohexyl)-4-cyclohexylpentan-2-one;
- 1-(4-*t*-Butylcyclohexyl)-5-(4-isopropylcyclohexyl)-pentan-3-one;
- 2-(3-Methylcyclohexenyl)-8-(2-isopropylcyclohexyl)-octan-4-one;
- 1-(2,6-Dimethyl-4-*t*-butylcyclohexyl)-5-(3,5-diethylcyclohexyl)pentan-3-one.

Preparation E

Preparation of N-(3-Aminopropyl)-1,4-cyclohexanebis(methylamine)

Acrylonitrile (26.5 g., 0.5 mole) is added dropwise over a 45-minute period to 1,4-cyclohexanebis(methylamine) (2.84 g., 2.0 mole) with stirring and ice-bath cooling. After complete addition, the reaction mixture is stirred for an additional 1 hour at 5°C., gradually warmed to 45°C. and kept for 2 hours at that temperature followed by 1 hour at 90°C. The reaction mixture is stripped of any unreacted acrylonitrile and excess of non-cyanoethylated bis(methylamine) starting material, which is removed at an internal temperature of 110°C. and 1 mm. The residue is then dissolved in 1.5 l. of ethyl alcohol (ammonia gas saturated) mixed with 50 ml. of sponge nickel catalyst and hydrogenated at 150 psi. After removal of catalyst by filtration, the solvent and ammonia are stripped off and the triamine product purified by fractionation under reduced pressure.

A higher homologue, N-(3-aminopropyl)-1,4-cyclohexanebis(2-ethylamine), is synthesized using the above procedure with 1,4-bis(2-aminoethyl)cyclohexane prepared according to P. P. Garcia and J. H. Wood, *J. Org. Chem.*, 26, 4167 (1961). Excess of starting amine in this example may be separated from product at a boiling point of 122°C.—126°C./1 mm.

Preparation F

Preparation of N-(3-Aminopropyl)-N'-(2-hydroxyethyl)-1,4-cyclohexanebis(methylamine)

Acrylonitrile (10.6 g., 0.2 mole) is added dropwise over a 15-minute period to N-(2-hydroxyethyl)-1,4-cyclohexanebis(methylamine) (37.2 g., 0.4 mole) with stirring and ice-bath cooling. After complete addition, the reaction mixture is stirred for an additional 2 hours at 5°C., allowed to gradually warm over a 1-hour period, and heated for 2 hours at 45°C. and finally, for 1 hour at 90°C. It is then fractionated under reduced pressure up to an internal temperature of 170°C. The residue is dissolved in 200 ml. of ethyl alcohol, cooled in an ice bath and saturated with ammonia gas at 0°C. Approximately 5 ml. of sponge nickel catalyst (W. R. Grace Co., Davison Chem. Division) is added and the mixture is shaken under hydrogen at 150 psi until no further hydrogen is taken up. The catalyst is removed by suction-filtration under nitrogen, the solvent is stripped away and the residue is fractionally distilled under reduced pressure. The triamine product is readily distinguished from cyanoethylated diamine by its lower *R_f* on silica gel using a solution of 1 volume concentrated aqueous ammonium hydroxide in 4 volumes methyl alcohol. The synthesis is an adaptation of the method of M. Israel et al, *J. Med. Chem.*, 7, 710 (1964) for the preparation of polymethylenepolyamines.

Preparation G

Preparation of N-(2-Hydroxyethyl)-1,4-cyclohexanebis(methylamine)

A solution of 14.2 gm. (0.1 mole) of 1,4-cyclohexanebis(methylamine) in 150 ml. anhydrous methyl alcohol and under an atmosphere of nitrogen is warmed to 45°C.—

50°C. In a 20-minute period, there is introduced with good agitation and beneath the liquid surface a total of 1.1 gm. (0.025 mole) of ethylene oxide in gaseous form. The reaction temperature is maintained at 45°C.—50°C. for an additional half hour after stopping the addition of ethylene oxide. The methyl alcohol is removed by distillation at atmospheric pressure; excess of 1,4-cyclohexanebis(methylamine) is readily separated from the product by fractionation under reduced pressure. Only monoethoxylated compound remains: it can be used as such or further purified by distillation at reduced pressure.

Preparation H

Preparation of N-(3-Amino-2-hydroxypropyl)-1,4-cyclohexanebis(methylamine)

1,4-Cyclohexanebis(methylamine) (14.2 g., 0.1 mole) is dissolved in 50 ml. of anhydrous methyl alcohol and the solution is cooled to +5°C. in an ice bath. Epichlorohydrin (9.3 g., 0.1 mole) is added in a 2-minute period and the temperature is maintained at +5°C. for 2 hours; reaction is allowed to continue at 10°C.—15°C. until thin layer chromatography of a portion (silica gel plate with development using a solution of 1 volume of concentrated aqueous ammonium hydroxide in 4 volumes of methyl alcohol) indicates nearly complete conversion of the starting diamine to the propylene chlorohydrin. The solution is then added to 100 ml. of dry methyl alcohol previously saturated to 0°C. with dry ammonia gas by continuous dropwise flow at +5°C. with good agitation and external cooling. After being stirred for 2 hours at +5°C., it is allowed to warm to 20°C. and mixed overnight. The reaction is completed by heating at 45°C.—55°C. for 6 hours. The solvent and ammonia are removed by stripping and the product is purified using fractional distillation under reduced pressure.

N-(2,3-Dihydroxypropyl)-1,4-cyclohexanebis(methylamine) is produced by alkaline hydrolysis of the above propylenechlorohydrin derivative.

The propylene chlorohydrin derivative is dissolved in a 1M sodium hydroxide solution containing 50% methyl alcohol and 50% water by weight in a ratio of 5 grams of chlorohydrin to 25 ml. of sodium hydroxide solution. After stirring for 24 hours at 20°C. the methyl alcohol is removed by distillation and the oil that separates is extracted with 100 ml. of diethyl ether. The extract is washed with approximately 10 ml. of cold water and the ethereal layer dried over anhydrous sodium sulphate and then filtered. Removal of the ether by distillation leaves the product in good purity as an oil.

Preparation I

Preparation of N,N'-bis-(3-Aminopropyl)-1,4-bis-(2-aminoethyl)cyclohexane

Acrylonitrile (10.6 g., 0.2 mole) is added dropwise over a 15-minute period to 1,4-bis-(2-aminoethyl)cyclohexane (17.0 g., 0.1 mole) cooled in an ice bath and with good stirring. The resultant solution is maintained at 5°C.—10°C. with agitation for 1 hour, allowed to warm to 25°C. over a 2-hour period and finally heated at 90°C.—95°C. for 4 hours. The reaction mixture is then freed of any unreacted material and monocyanoethylated product by gradually heating to an internal temperature of 130°C. at a pressure of 0.5—1 mm. The residue is dissolved in 200 ml. ethyl alcohol, which had been previously saturated with dry ammonia gas at 0°C., mixed with approximately 5 ml. of a sponge nickel catalyst suspension and reduced with shaking under 200 psi hydrogen. The catalyst is removed by suction filtration, the filtrate stripped of solvent and the residue purified by fractional distillation under reduced pressure.

Preparation J

Preparation of N-(2-Aminoethyl)-1,4-bis-(2-aminoethyl)cyclohexane

1,4-Bis-(2-aminoethyl)cyclohexane (68 gm., 0.4 mole) and ethyleneimine (4.3 gm., 0.1 mole) with 0.4 g. ammonium chloride are mixed in a glass-lined pressure reactor, which is then filled with nitrogen to 100 psi. The mixture is shaken and heated at 85°C.—95°C. for 48 hours. After cooling, it is distilled rapidly free of the salt and then fractionated under high vacuum. The starting diamine is readily distinguished from the triamine product by thin-layer chromatography on silica gel using a mixture of 1 volume of concentrated aqueous ammonium hydroxide with 4 volumes of methyl alcohol, the diamine having a much higher R_f .

Preparation K

N,N-Bis-(3-hydroxypropyl)-1,4-cyclohexanediis(methylamine)

Preparation of 1-Cyano-4-[di-(3-hydroxypropyl)aminomethyl]cyclohexane and catalytic reduction

5 a. 1-Bromomethyl-4-cyanocyclohexane (20.2 g., 0.1 mole) and di-(3-hydroxypropyl)amine (53.2 g., 0.4 mole) in 400 ml. of anhydrous isopropyl alcohol are heated in an autoclave at 105°C.—115°C. for 8 hours with continuous agitation. The reaction mixture is stripped of solvent under reduced pressure and the residue diluted with 500 ml. of ice water. A cold solution of 5 g. of sodium hydroxide in 100 ml. of water is added and the mixture extracted with two 150-ml. portions of methylene chloride. The organic phase is then washed with 50 ml. of ice water, dried overnight with anhydrous sodium sulfate, filtered and freed of solvent by distillation under reduced pressure.

10 b. The residual oil from a.) is taken up in 200 ml. of anhydrous ethyl alcohol previously saturated at 0°C. with dry ammonia gas, mixed with 5 ml. of sponge nickel catalyst suspension and hydrogenated at 25°C. under 100 psi hydrogen pressure in a stirred autoclave. The reaction completion is readily determined by disappearance of the C≡N IR absorption band and measurement of hydrogen uptake. The catalyst is removed by suction filtration, the solvent is removed by mild heating under reduced pressure and the product is obtained pure with fractional distillation at reduced pressure.

Preparation L

N,N-Di-(2,3-dihydroxypropyl)trimethylenediamine

25 Bis-(2,3-dihydroxypropyl)amine (16.5 g., 0.1 mole) and acrylonitrile (6.4 g., 0.12 mole) are mixed in an ice bath and then warmed to room temperature. After standing for 2 hours, the mixture is then heated at 45°C.—55°C. for 3 hours. The excess of acrylonitrile is removed by gentle warming under reduced pressure. The residue is taken up in ethyl alcohol, mixed with sponge nickel catalyst and hydrogenated under 200 psi hydrogen using good agitation. After filtration of catalyst the solvent and excess of acrylonitrile are removed by stripping under reduced pressure to leave the product as an oil.

Preparation M

N,N,N'-Tri-(2,3-dihydroxypropyl)trimethylenediamine

35 N,N-di-(2,3-dihydroxypropyl)trimethylenediamine (11.1 g., 0.05 mole) is dissolved in 125 ml. of methanol and the solution is heated under reflux with agitation. Glycidyl (3.7 g., 0.05 mole) is added dropwise over a period of 1.5 hour and the solution is mixed for an additional hour at 60°C.—80°C. The methyl alcohol and other volatiles are removed by stripping under reduced pressure to leave the product suitable for use in the next steps.

Preparation N

5,9,9-Tri-(2,3-dihydroxypropyl)-1,5,9-triazanonane

40 A portion of the residual oil from Preparation M (5.9 g., 0.02 mole) is mixed with acrylonitrile (2.75 g., 0.05 mole) at room temperature and then warmed at 50°C.—60°C. for 10—15 hours. The excess of acrylonitrile is removed by stripping under reduced pressure and the residual oil is taken up in 50 ml. of ethanol, mixed with 2 g. of sponge nickel catalyst and shaken under a hydrogen atmosphere of 200 psi for 6 hours. The mixture is filtered free of catalyst and the solvent removed by distillation. The product can be brought to analytical purity by chromatography on a silica gel column and is an oil.

EXAMPLE 1

Preparation of 1-[1,5-Di-(4-isopropylcyclohexyl)-3-pentyl]-1,5,9-triazanonane

50 1,5-Di-(4-isopropylcyclohexyl)-3-pentanone (6.70 g., 0.02 mole) and 3,3'-iminobispropylamine (13.1 g., 0.10 mole) in 150 ml. toluene are heated at reflux overnight with a Dean-Stark water separator. The cooled solution is concentrated under reduced pressure. The residue is dissolved in ethanol and hydrogenated with PtO₂ at room temperature and 40 psi hydrogen pressure. The platinum catalyst is filtered off and the ethanol removed under vacuum. The residual oil is dissolved in ether and the ethereal solution washed several times with water to remove the excess of 3,3'-iminobispropylamine. The ethereal extracts are dried over anhydrous sodium sulfate and concentrated under vacuum to leave the polyamine as a colorless oil.

The oil is dissolved in ether and hydrogen chloride gas is bubbled into the solution until no further precipitation occurs. The ether is evaporated under reduced pressure to leave the product as a solid which is digested with hot isopropyl alcohol. The solids are collected by filtration and dried under vacuum at 70°C. to give a colorless product, 1-[1,5-di-(4-isopropylcyclohexyl)-3-pentyl]-1,5,9-triazanonane trihydrochloride.

In an analogous manner, from the ketones and the amines set forth below, there are prepared the following compounds of this invention:

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TABLE I

Ketone	Amine	Product	Melting Point
1,9-Dicyclohexyl-5-nonanone	3,3'-Iminobispropylamine	1-[[1,9-Dicyclohexyl-5-nonyl]-1,5,9-triazanonane trihydrochloride	Dec. 183°—187°C. to pulp; 255°—267°C. to liquid
1,5-Dicyclohexyl-3-pentanone	Ethylenediamine	N-[[1,5-Dicyclohexyl-3-pentyl]-ethylenediamine dihydrochloride	261°—263°C.
1,5-Dicyclohexyl-3-pentanone	N-(3-Aminopropyl)-N-methyl-1,3-propanediamine	1-[[1,5-Dicyclohexyl-3-pentyl]-5-methyl-1,5,9-triazanonane trihydrochloride	247°—249°C.
1,3-Dicyclohexylacetone	2-Hydroxy-1,3-diaminopropane	N-[[1,3-Dicyclohexyl-2-propyl]-2-hydroxy-1,3-diaminopropane dihydrochloride	Melts 200°C. with softening from 147°C.
1,5-Dicyclohexyl-3-pentanone	1,3-Diaminopropane	N-[[1,5-Dicyclohexyl-3-pentyl]-trimethylenediamine dihydrochloride	245°—250°C.
1,5-Dicyclohexyl-3-pentanone	2-Hydroxy-1,3-diaminopropane	1-Amino-3-[[1,5-dicyclohexyl]-3-pentylamino]-2-propanol dihydrochloride	250°—252°C.
1,7-Dicyclohexyl-4-heptanone	Iminobispropylamine	1-(1,7-Dicyclohexyl-4-heptyl)-1,5,9-triazanonane trihydrochloride	260°—261°C.
1,5-Dicyclohexyl-3-pentanone	Iminobispropylamine	1-(1,5-Dicyclohexyl-3-pentyl)-1,5,9-triazanonane trihydrochloride	Dec. 224°—228°C. to pulp; 242°—246°C. to liquid
1,5-Dicyclohexyl-3-pentanone	Triethylenetetramine	1-(1,5-Dicyclohexyl-3-pentyl)-1,4,7,10-tetraazadecane	

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EXAMPLE 2

Preparation of 1-[1,5-Di-(4-isopropylcyclohexen-1-yl)-3-pentyl]-1,5,9-triazanonane
1,5-(4-isopropylcyclohexen-yl)-3-pentanone, (6.60 g., 0.02 mole) and 3,3'-imino-
bispropylamine (13.1 g., 0.10 mole) in 150 ml. of toluene is heated at reflux overnight
with a Dean-Stark water separator. The toluene is then removed under vacuum. The
residual oil, dissolved in 25 ml. isopropanol, is added dropwise to sodium borohydride
(1.90 g., 0.05 mole, excess) suspended in 50 ml. isopropanol. After complete addition,
the reaction mixture is heated at reflux for one hour. The isopropanol is evaporated
under reduced pressure, the residue treated with water and the aqueous mixture
extracted well with ether. The combined ether extracts are back-washed with
water and a saturated sodium chloride solution, dried over anhydrous sodium
sulfate and concentrated under vacuum to leave the polyamine product as a clear oil
7.4 g. (90%).

The oil is dissolved in ether and the solution cooled in an ice-water bath.
Hydrogen chloride gas is bubbled into the solution until no further precipitate is
formed. The solid is collected by filtration, washed with a small amount of ether, and
dried under vacuum to leave the polyamine trihydrochloride as a colorless product
(96%), m.p. 256°—257°C.

In an analogous manner, using the ketones and the amines set forth below,
the following compounds of this invention are prepared.

TABLE II

Ketone	Amine	Product	Melting Point
1,7-Di-(cyclohex-3-enyl)-4-heptanone	Iminobispropylamine	1-[1,7-Di-(cyclohex-3-enyl)-4-heptyl]-1,5,9-triazanonane trihydrochloride	222°—223°C.
2,8-Di-(4-methylcyclohex-3-enyl)-5-nonanone	Iminobispropylamine	1-[2,8-Di-(4-methylcyclohex-3-enyl)-5-nonyl]-1,5,9-triazanonane trihydrochloride	269°—271°C.
1,5-Di-[4-(isopropyl)cyclohex-1-enyl]-3-pentanone	Triethylenetetramine	1-[1,5-Di-(4-isopropylcyclohex-1-enyl)-3-pentyl]-1,4,7,10-tetrazadecane tetrahydrochloride	229°—230°C.
2,8-Di-(4-methylcyclohex-3-enyl)-5-nonanone	Tris-(3-aminopropyl)-amine	1-[2,8-Di-(4-methylcyclohex-3-enyl)-5-nonyl]-5-(3-aminopropyl)-1,5,9-triazanonane	
1,7-Di(cyclohex-3-enyl)-4-heptanone	1,4-Bis-(3-aminopropyl)- piperazine	1-(3-Aminopropyl)-4-[3-[1,7-di-(cyclohexen-3-yl)-4-heptylamino]propyl]piperazine	
1,7-Di(cyclohex-3-enyl)-4-heptanone	1,4-Di(3-aminopropyl)- piperidine	A mixture of 1-(3-aminopropyl)-4-[3-[1,7-di-(cyclohexen-3-yl)-4-heptylamino]propyl]piperidine and 1-[3-[1,7-di-(cyclohexen-3-yl)-4-heptylamino]propyl]-4-(3-aminopropyl)piperidine	
1,5-Di-(4-isopropylcyclohexenyl)-3-pentanone	N,N'-bis(2-aminoethyl)- 1,3-propanediamine	1-[1,5-Di-(4-isopropylcyclohexenyl)-3-pentyl]-1,4,8,11-tetrazadecane	

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EXAMPLE 3

1-[1,7-Di-(4-methylcyclohexyl)-4-heptyl]-1,4,8-triazaoctane

A mixture of 1,7-di-(4-methylcyclohex-3-enyl)-4-heptanone (0.03 mole) and 1,2-diaminoethane (12.0 g., 0.20 mole) in 250 ml. ethanol is heated at reflux overnight. The cooled reaction mixture is hydrogenated with PtO₂ at room temperature and 40 psi hydrogen pressure. The platinum catalyst is filtered off and the ethanol removed under reduced pressure. The residual oil is dissolved in ether and the ethereal solution washed several times with water to remove the excess of diaminoethane. The ethereal extracts are dried over anhydrous sodium sulfate and concentrated under vacuum to leave a colorless oil, 11.2 g. (100%).

The oil is dissolved in 20 ml. tert-butanol and chilled to 0°C.—5°C. in an ice-water bath. Acrylonitrile (1.75 g., 2.2 ml., 0.033 mole) is added dropwise over a 5-minute period. The reaction mixture is allowed to warm up to room temperature and is then heated at 60°C. overnight. The t-butanol is removed under reduced pressure. The residual oil is dissolved in 150 ml. glacial acetic acid and hydrogenated with PtO₂ at room temperature and 40 psi hydrogen pressure. The platinum catalyst is filtered off and the acetic acid removed under vacuum. The residue is dissolved in ether and made basic with 10% sodium hydroxide. The ethereal solution is washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave the product.

In addition, the compounds of this invention set forth below are prepared by the reactions set forth in the previous Examples.

1 - [1,9 - Dicyclohexyl - 5 - nonyl] - 1,5,8,12 - tetrazadodecane from N,N' - bis - (3 - aminopropyl) - 1,2 - ethanediamine and 1,9 - dicyclohexyl - 5 - nonanone;

1 - [1,5 - Dicyclohexyl - 3 - pentyl] - 10 - (2 - hydroxyethyl) - 1,4,7,10 - tetrazadecane from 1 - (2 - hydroxyethyl) - 1,4,7,10 - tetrazadecane and 1,5 - dicyclohexyl - 3 - pentanone;

1 - [1,5 - Dicyclohexyl - 3 - pentyl] - 4 - (2 - aminoethyl) - 1,4,7 - triazaheptane from tris - (2 - aminoethyl)amine and 1,5 - dicyclohexyl - 3 - pentanone;

1 - [1,5 - Dicyclohexyl - 3 - pentyl] - 5 - (2 - hydroxypropyl) - 9 - hydroxymethyl - 1,5,9 - triazanone from 1 - hydroxy methyl - 5 - (2 - hydroxypropyl) - 1,5,9 - triazanone and 1,5 - dicyclohexyl - 3 - pentanone;

EXAMPLE 4

Preparation of 1-[1,5-Di-(4-isopropylcyclohexyl)-3-pentyl]-5-(2,3-dihydroxypropyl)-1,5,9-triazanonane

1,5-Di-(4-isopropylcyclohexyl)-3-pentanone (6.7 g., 0.02 mole) and 3,3'-(2,3-dihydroxypropylimino)bispropylamine (20.5 g., 0.10 mole), (obtained by the catalytic hydrogenation of dicyanoethylated glycerylamine), in 150 ml. of toluene is heated at reflux overnight with a Dean-Stark water separator. The cooled solution is concentrated under reduced pressure. The residue is dissolved in ethanol and hydrogenated with PtO₂ at room temperature and 40 psi hydrogen pressure. The platinum catalyst is filtered off and the ethanol removed under vacuum. The residual oil is dissolved in ether and the ethereal solution washed several times with water to remove the excess of 3,3'-(2,3-dihydroxypropylimino)bispropylamine. The ethereal extracts are dried over anhydrous sodium sulfate and concentrated to leave the polyamine product as an oil.

In a like manner and using analogous quantities, but using N,N-di-(2,3-dihydroxypropyl)trimethylenediamine and 5,9,9-tri-(2,3-dihydroxypropyl)-1,5,9-triazanonane instead of 3,3'-(2,3-dihydroxypropylimino)bispropylamine there are prepared respectively N - [1,5 - di - (4 - isopropylcyclohexyl) - 3 - pentyl] - N' - di - (2,3 - dihydroxypropyl)trimethylenediamine and 1 - [1,5 - di - (4 - isopropylcyclohexyl) - 3 - pentyl] - 5 - (2,3 - dihydroxypropyl)9 - di - (2,3 - dihydroxypropyl) - 1,5,9 - triazanone.

EXAMPLE 5

Preparation of 1-[1,5-Di-(4-isopropylcyclohexyl)-3-pentyl]-5-(2,3-dihydroxypropyl)-9-(1,3-dihydroxyl-2-propyl)-1,5,9-triazanonane

1 - [1,5 - Di - (4 - isopropylcyclohexyl) - 3 - pentyl] - 5 - (2,3 - dihydroxypropyl) - 1,5,9 - triazanone (5.2 g., 0.01 mole) and 1,3-dihydroxyacetone (9 g., 0.1 mole) in 100 ml. of chloroform is heated at reflux with a water separator connected until 1.8 ml. of water is collected (8—12 hours). The chloroform and excess of 1,3-dihydroxyacetone are removed by distillation under reduced pressure. The residual oil is taken up in 75 ml. of ethanol, mixed with 1 gm. of platinum oxide and hydrogenated at 40 psi hydrogen pressure with shaking at room temperature. The catalyst

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is removed by filtration and ethyl alcohol by distillation to leave an oil. The product is purified by column chromatography using silica gel and development with methyl alcohol containing ammonium hydroxide.

In an analogous manner but starting with 1,7 - di - (2,3 - dimethylcyclohexyl - 4 - heptyl)ethylenediamine, instead of 1 - [1,5 - di - (4 - isopropylcyclohexyl) - 3 - pentyl] - 1,5,9 - triazanone, there is obtained N - [1,7 - di - (2,3 - dimethylcyclohexyl) - 4 - heptyl - N' - (1,3 - dihydroxy - 2 - propyl)ethylenediamine.

EXAMPLE 6

1 - [1,7 - Di - (4 - methylcyclohexyl) - 4 - heptyl] - 4,8,8 - tri - (2,3 - dihydroxypropyl) - 1,4,8 - triazaoctane

1 - [1,7 - Di - (4 - methylcyclohexyl) - 4 - heptyl] - 1,4,8 - triazaoctane (4.1 g., 0.01 mole) is dissolved in 50 ml. of methanol and heated under reflux with agitation. Glycidol (15 g., 0.2 mole) is added dropwise over a period of 1.5 - 2 hours. After complete addition, the reaction mixture is stirred for an additional 2 hours at 90°C. - 100°C. The methyl alcohol is removed by stripping under reduced pressure and excess of glycidol by distillation at 1 mm pressure. The residue is further purified by conversion to the trihydrochloride salt in ethyl alcohol with dry hydrogen chloride and fractional crystallization. The free base may then be liberated from its salt by resin ion-exchange or neutralization with aqueous sodium hydroxide.

In an analogous manner using the following dicyclohexyl polyamines, there are obtained the following products.

Dicyclohexyl Polyamine

1 - [1,5 - Di - (4 - isopropylcyclohexyl - 3 - pentyl) - 2,7 - dihydroxy - 1,5,9 - triazanone

1 - [1,5 - Di - (4 - isopropylcyclohexyl - 3 - pentyl) - 1,4,7 - triazaheptane

1 - [1,5 - Di - (4 - isopropylcyclohexyl - 3 - pentyl) ethylenediamine

Product

1 - [1,5 - Di - (4 - isopropylcyclohexyl - 3 - pentyl) - 2,7 - dihydroxy - 5 - (2,3 - dihydroxypropyl) - 9,9 - di - (2,3 - dihydroxypropyl) - 1,5,9 - triazanone

1 - [1,5 - Di - (4 - isopropylcyclohexyl - 3 - pentyl) - 4 - (2,3 - dihydroxypropyl) - 7,7 - di - (2,3 - dihydroxypropyl) - 1,4,7 - triazaheptane

N - [1,5 - Di - (4 - isopropylcyclohexyl - 3 - pentyl) - N', N' - di - (2,3 - dihydroxypropyl) - ethylenediamine

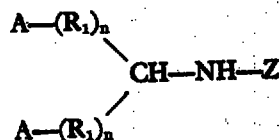
Also each of the respective ketones IV set forth in Preparations C and D when reacted with each of the individual amines set forth hereinbefore, firstly according to the method set forth in Example 1 and secondly according to the method set forth in Example 2, produce a range of compounds of Formula I.

Moreover, salts other than the various specified hydrochlorides can be prepared by choice of acid, and the free bases regenerated from the salts by methods indicated in Example 6.

Compounds that can be prepared in this way include salts of (1,5 - dicyclohexyl - 3 - pentyl) - 1,5,9 - triazanone, (1,5 - dicyclohexyl - 3 - pentyl) - 1,4,7,10 - tetrazadecane and 1 - (1,5) - di - (4 - isopropylcyclohexyl - 3 - pentyl) - 1,5,9 - triazanone; (1,7 - dicyclohexyl - 4 - heptyl) - 1,5,9 - triazanone and its salts; the dipropionate salt of 1 - (1,5 - dicyclohexyl - 3 - pentyl) - 3 - hydroxy - 1,5 - diazapentane and the free base forms of 1 - [1,5 - di - (4 - isopropylcyclohexyl - 1 - pentyl) - 3 - pentyl] - 1,5,9 - triazanone, 1 - [1,5 - di - (4 - isopropylcyclohexyl - 1 - pentyl) - 3 - pentyl] - 1,4,7,10 - tetrazadecane and 1 - [2,8 - di - (4 - methylcyclohex - 3 - enyl) - 5 - nonyl] - 1,5,9 - triazanone.

WHAT WE CLAIM IS:—

1. A compound having the formula:



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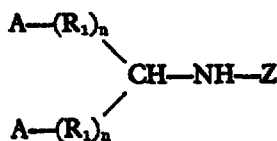
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* C L H S *

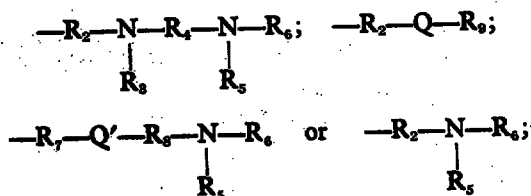
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where each A, independently of the other, is a cyclohexyl, (C₁₋₆ alkyl)-substituted cyclohexyl, cyclohexenyl or (C₁₋₆ alkyl)-substituted cyclohexenyl radical; each n, independently of the other, is 0 or 1; each R₁, independently of the other, is C₁₋₄ alkylene and Z is a radical of formula

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where Q is 1,4-piperidinediyl or 1,4-piperazinediyl; Q' is 1,4-cyclohexylene; each of R₂ and R₄ is 2-hydroxy-1,3-trimethylene or C₁₋₄ alkylene; R₃ is hydrogen, C₁₋₄ alkyl, C₂₋₄ aminoalkyl, C₁₋₄ hydroxyalkyl or C₂₋₄ dihydroxyalkyl; R₅ is hydrogen, aminoethyl aminopropyl, C₁₋₄ monohydroxyalkyl, or C₂₋₄ dihydroxyalkyl; R₆ is hydrogen, C₁₋₄ monohydroxyalkyl or C₂₋₄ dihydroxyalkyl; R₇ is 2-hydroxy-1,3-trimethylene, C₁₋₄ alkylene or a chemical bond between the cyclohexylene residue and a first nitrogen; R₈ is 2-hydroxy-1,3-trimethylene, C₁₋₄ alkylene or a chemical bond between the cyclohexylene residue and a second nitrogen; and R₉ is aminoethyl, aminopropyl, or aminohydroxypropyl.

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2. A compound as claimed in Claim 1, in which n is 1 and R₁ is methylene.

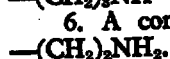
3. A compound as claimed in Claim 1, in which n is 1 and R₁ is ethylene.

4. A compound as claimed in Claim 1, in which n is 1 and R₁ is trimethylene.

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5. A compound as claimed in any one of Claims 1 to 4, in which Z is

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7. A compound as claimed in any one of Claims 1 to 4, in which Z is



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8. A compound as claimed in any one of Claims 1 to 4, in which Z is

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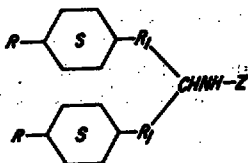
9. A compound as claimed in any one of Claims 1 to 4, in which Z is CH₂CHOHCH₂NH₂.

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10. A compound as claimed in any one of Claims 1 to 4, in which Z is (CH₂)₃NH₂.

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11. A compound of the formula:



in which

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R is hydrogen, methyl or isopropyl;

R₁ is methylene, ethylene, trimethylene or tetramethylene;

and Z is:

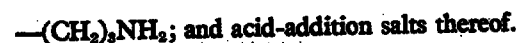
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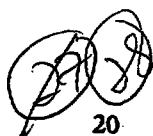


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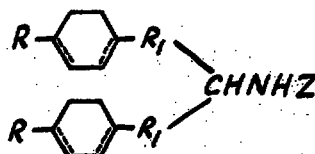


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12. 1-(1,5-Dicyclohexyl-3-pentyl)-1,5,9-triazanonane and salts thereof.
13. 1-(1,7-Dicyclohexyl-4-heptyl)-1,5,9-triazanonane and salts thereof.
14. 1-(1,5-Dicyclohexyl-3-pentyl)-1,4,7,10-tetrazadecane and salts thereof
15. 1-(1,5)-Di-(4-isopropylcyclohexyl-3-pentyl)-1,5,9-triazanonane and salts thereof.
16. 1-(1,5-Dicyclohexyl-3-pentyl)-3-hydroxy-1,5-diazapentane and salts thereof.
17. A dihydrochloride acid-addition salt as claimed in Claim 16.
18. A dipropionate salt as claimed in Claim 16.
19. N-(1,5-Dicyclohexyl-3-pentyl)ethylenediamine.
20. A dihydrochloride acid-addition salt as claimed in Claim 19.
21. A compound of the formula:

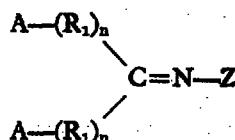


where

- R is hydrogen, methyl or isopropyl;
R₁ is C₁ to C₆ alkylene;
the dashed line indicates cyclohexenyl or cyclohex-3-enyl;
and Z is

- (CH₂)₂NH(CH₂)₂NH₂;
—(CH₂)₂NH(CH₂)₂NH(CH₂)₂NH₂;
—(CH₂)₂NCH₂(CH₂)₂NH₂;
—CH₂CHOHCH₂NH₂;
—(CH₂)₂NH₂; and
—(CH₂)₂NH₂; and acid addition salts thereof.

22. 1 - [1,5 - Di - (4 - isopropylcyclohexen - 1 - yl) - 3 - pentyl] - 1,5,9 - triazanonane.
23. 1 - [1,5 - Di - (4 - isopropylcyclohexen - 1 - yl) - 3 - pentyl] - 1,4,7,10 - tetrazadecane.
24. 1 - [2,8 - Di - (4 - methylcyclohex - 3 - enyl) - 5 - nonyl] - 1,5,9 - triazanonane.
25. A method of preparing a compound as claimed in Claim 1, comprising chemically or catalytically reducing a Schiff base of the formula:



where A, R, n and Z are as defined in Claim 1.

26. A method of preparing a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1 to 6.
27. A compound according to Claim 1 when prepared by a method as claimed in Claim 25 or 26.
28. A method of inhibiting the growth of susceptible micro-organisms and algae on or within a host or substrate comprising applying an inhibiting amount of a compound as claimed in any one of Claims 1 to 24 and 27.
29. A composition for inhibiting the growth of susceptible micro-organisms and algae comprising a compound as claimed in any one of Claims 1 to 24 and 27 and a carrier.
30. A composition as claimed in Claim 29, in which the carrier is a solid diluent.



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31. A natural or synthetic fibre bearing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
32. An oil-well drilling mud or secondary oil recovery water or brine containing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
33. A fluid for use in cutting or grinding operations containing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
34. Paints or coatings, pigment suspensions and adhesives containing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
35. Fabrics bearing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
36. Fabrics as claimed in Claim 35, in the form of diapers, surgical masks, caps, gowns, towels and drapes, covers for hospital furniture and instrument wrappings, aseptic facial tissues, sanitary napkins or bathroom tissue.
37. A soap or detergent for use in cleaning the skin containing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
38. Impounded water containing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
39. A wettable powder for agricultural use containing as antimicrobial agent a compound as claimed in any one of Claims 1 to 24 and 27.
40. An aqueous suspension, dispersion or emulsion containing a compound as claimed in any one of Claims 1 to 24 and 27.

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