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Berezin et al.

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[54] 2,5-DIPHENYLCYCLOALIPHATIC ALKYLAMINES

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[52] **U.S. Cl.**..... **260/570.5 CA**, 260/456 R, 260/465 R, 260/544 M, 260/557 B, 260/570.8 R, 260/570.9, 260/599, 106/15 R, 252/110, 424/330
[51] **Int. Cl.**..... **C07c 87/28**
[58] **Field of Search** 260/570.9, 570.5; 424/330

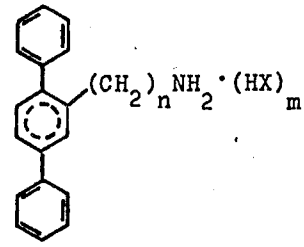
[56] **References Cited**
UNITED STATES PATENTS

3,652,589 3/1972 Flick et al..... 260/570.5

Primary Examiner—Robert V. Hines

[57] **ABSTRACT**

Compounds of the following formula are useful as bactericides:



where

represents a ring containing 6 carbon atoms and having 0 to 3 double bonds; *n* is 1 or 2; *m* is 0, ½ or 1; and X is halogen, sulfate, or bisulfate.

An exemplary species of the above compound is 2,5-diphenylcyclohexenylmethylamine hydrochloride.

3 Claims, No Drawings

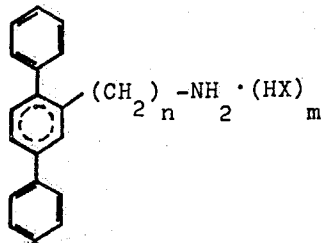
2,5-DIPHENYLCYCLOALIPHATIC ALKYLAMINES

BACKGROUND OF THE INVENTION

Chemical compounds having bactericidal activity have been used in pharmaceutical, cosmetic, and industrial applications. However, in recent years the use of bactericides such as the mercurials, hexachlorophene and chlorinated phenols are being restricted because of toxicity problems. Thus, there is a need for the development of new bactericides for such uses which do not have toxicity problems.

SUMMARY OF THE INVENTION

We have discovered that the compounds represented by the following formula are useful bactericides:

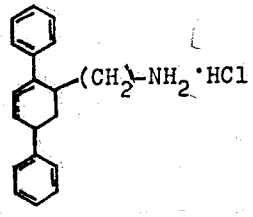


In the above formula the symbol

represents a ring containing 6 carbon atoms and having 0 through 3 double bonds, *n* is 1 or 2, *m* is 0, ½ or 1, and X is chlorine, sulfate, or bisulfate.

In view of their physical properties, the compounds where *n* is 1 are preferred.

The most preferred compound is 2,5-diphenylcyclohexenylmethylamine hydrochloride. This compound is believed to have the following structure



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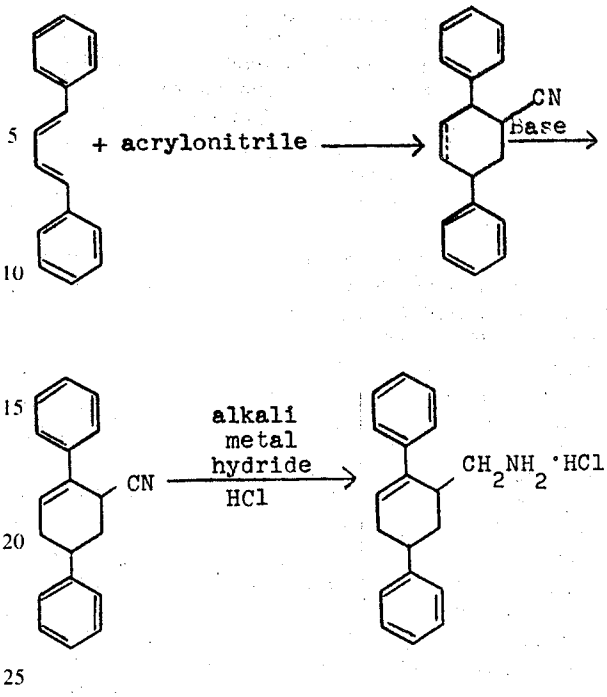
however, the exact position of the double bond in the middle ring is not presently known. Data examined to date indicates that it probably is in the position illustrated above, however, it could be located in the position indicated by the dotted line.

DESCRIPTION OF THE INVENTION

The compounds of the invention can be prepared according to the following reaction scheme which illustrates the preparation of the preferred compound.



The starting materials for the preparation of the compounds of the invention can be synthesized using the Diels-Alder reaction. Reaction of 1,4-diphenylbutadiene with acrylonitrile or acrolein gives 2,5-diphenylcyclohexenylcarbonitrile or -carboxaldehyde, respectively. Preparation of 2,5-diphenylcyclohexane-cis- and trans-carboxylic acids via the Diels-Alder reaction is described in the literature [Ann.571, 87 (1950)]. Temperatures and times for these Diels-Alder reaction can range from 100° to 200°C. and from 10 to 30 hours. The reactions can occur with or without solvent. If desired, solvents such as benzene, toluene and xylene can be employed.

The double bond of 2,5-diphenylcyclohexenylcarbonitrile can be isomerized with base. Strong bases such as alkali metal alkoxides are preferred, although other bases such as sodium amide, alkyl lithiums or sodium hydride can be used. The 2,5-diphenylcyclohexenylcarbonitriles can then be reduced to 2,5-diphenylcyclohexenylmethylamines with an alkali metal hydride, such as lithium aluminum hydride.

The 2,5-diphenylcyclohexenylcarboxaldehydes can be reduced to 2,5-diphenylcyclohexenylmethanol with an alkali metal hydride, such as sodium borohydride. The hydroxyl group of the alcohol can be converted into a leaving group such as tosylate, mesylate or brosylate by reaction with the appropriate sulfonic acid halide, such as p-toluenesulfonyl chloride. Conversion of the hydroxyl group into a halo group with a halide acid or thionyl chloride or bromide can also be accomplished.

Salts of the free amines of this invention can be formed by contacting the amine with the appropriate inorganic acid in a solvent and either collecting the salt by filtration or by evaporation of the solvent. The amine hydrochlorides may be conveniently prepared by treating an ethereal solution of the amine with dry hydrogen chloride.

The following examples illustrate the preparation of the compounds of the invention.

EXAMPLE No. 1

2,5-Diphenylcyclohexenylmethylamine hydrochloride

A mixture of 40 g (0.194 mol) of 1,4-diphenylbutadiene and 13.7 g (0.258 mol) of acrylonitrile with 1 g of hydroquinone was reacted at 190°C for 19 hrs. The reaction mixture was distilled to give 40 g of 2,5-diphenylcyclohexenylcarbonitrile, bp 0.25 = 190°C.

A solution of 8.8 g (33 mmol) of the above oil and 3 g (0.13 mol) of sodium in 88 ml of ethanol was heated at reflux overnight. The reaction mixture was cooled and then concentrated in vacuum. Water was added to the residue and the product was extracted into benzene. The organic solution, after drying over magnesium sulfate, was concentrated to 8.7 g of oil.

The 8.7 g of oil was dissolved in 50 ml of tetrahydrofuran and added dropwise to a stirred suspension of 5 g (0.13 mol) of lithium aluminum hydride in 150 ml of tetrahydrofuran. The reaction mixture was refluxed overnight and then cooled. Ether was added and the excess lithium aluminum hydride was destroyed with 20 percent aqueous sodium hydroxide. The liquid phase was decanted from the solid and the solid was washed with THF. The combined organic liquids were concentrated in vacuum and the residue was then dissolved in dry ether. The ether solution, after drying over potassium carbonate, was treated with dry hydrogen chloride. The precipitate was collected by filtration and was recrystallized from ethanol to give 2,5-diphenylcyclohexenylmethylamine hydrochloride as colorless crystals, mp >260°.

EXAMPLE No. 2

p-Terphenyl-2'-methylamine Hydrochloride

A solution of 2.3 g (8.4 mmol) of p-terphenyl-2'-carboxamide [J. Chem. Soc., 3480 (1957)] in 25 ml of glyme was added dropwise to a suspension of 2 g of lithium aluminum hydride in 75 ml of tetrahydrofuran and the reaction mixture was refluxed overnight. The excess lithium aluminum hydride was destroyed with 20 % aqueous sodium hydroxide and the liquid was concentrated in vacuum. The residue was dissolved in ether, and after drying over potassium carbonate, was treated with dry hydrogen chloride. The precipitate was collected by filtration to give 1.2 g of p-terphenyl-2'-methylamine hydrochloride as colorless crystals, mp >240°.

EXAMPLE NO. 3

2,5-Diphenylcyclohexenylmethylamine Hydrochloride

2,5-Diphenylcyclohexenylcarbonitrile (9 g, 24 mol) was reduced with lithium aluminum hydride according to the procedure described in the third paragraph of Example 1, to give 5.5 g of 2,5-diphenylcyclohexenylmethylamine hydrochloride as colorless crystals, mp >240°.

EXAMPLE NO. 4

2,5-Diphenylcyclohexane-trans-methylamine Hydrochloride

A solution of 10 g (35.7 mmol) of 2,5-diphenylcyclohexane-trans-carboxylic acid [Ann. 571, 87 (1950)] and 43 g (0.357 mol) of thionyl chloride was heated under reflux for 2 hrs., cooled and then concentrated in vacuum to give the corresponding acid chloride as an oil.

The acid chloride was treated in chloroform with gaseous ammonia and then the solvent was removed in vacuo. The residue was titurated with 10 percent aqueous potassium carbonate and ether and colorless crystals of 2,5-diphenylcyclohexane-trans-carboxamide, mp 137°–141°, were collected by filtration. One recrystallization from benzene gave 2.4 g of an analytical sample, mp 142.5°–144°.

The amide (2 g, 7.2 mmol) was reduced with lithium aluminum hydride according to the procedure described in the third paragraph of Example 1, to give 1.1 g of 2,5-diphenylcyclohexane-trans-methylamine hydrochloride, as colorless crystals, mp 210°–240° dec.

EXAMPLE NO. 5

2,5-Diphenylcyclohexane-cis-methylamine Hydrochloride

2,5-Diphenylcyclohexane-cis-carboxylic acid [Ann. 571, 87 (1950)] was converted to 2,5-diphenylcyclohexane-cis-carboxamide mp 155°–6.5°, according to the procedure described in Example 4.

The amide was reduced with lithium aluminum hydride according to the procedure described in the third paragraph of Example 1, to afford 2,5-diphenylcyclohexane-cis-methylamine hydrochloride as colorless crystals, mp 216°–220° dec.

EXAMPLE NO. 6

2,5-Diphenylcyclohexenylethylamine Hydrochloride

A mixture of 240 g (1.165 mol) of 1,4-diphenylbutadiene and 90 g (1.6 mol) of acrolein with 1 g of hydroquinone was reacted at 190°C for 19 hrs. The reaction mixture was distilled to give 248.3 g of 2,-5-diphenylcyclohexenylcarboxaldehyde, $bp_{0.5} = 172°C$.

A solution of 20 g (76.3 mol) of the aldehyde and 4 g (0.1 mol) of sodium borohydride in 100 ml of ethanol was stirred overnight at room temp and then poured onto water. The product was extracted into ether, which was washed with water, dried over magnesium sulfate and concentrated in vacuo to 19.2 g of 2,5-diphenylcyclohexenylmethanol, as a colorless oil.

The alcohol (19.2 g, 73 mmol) dissolved in 100 ml of pyridine was treated with 15.2 g (79.7 mmol) of p-toluenesulfonyl chloride at 0°C and then was stirred overnight at room temp. The reaction mixture was poured onto ice-water containing 150 ml of concentrated hydrochloric acid and the product was extracted into ether. The ether was dried over magnesium sulfate and removed in vacuum to yield 26.7 g of 2,5-diphenylcyclohexenylmethanol tosylate, as a colorless oil.

A solution of 26.7 g (63.6 mmol) of the tosylate and 6 g (0.123 mol) of sodium cyanide in 100 ml of dimethylsulfoxide was stirred overnight at room temp and then poured onto water. The product was extracted into ether, which was dried over magnesium sulfate and evaporated under vacuum to give 15 g of 2,5-diphenylcyclohexenylacetonitrile, as a colorless oil.

The nitrile was reduced with lithium aluminum hydride according to the procedure described in paragraph 3 of Example 1 to give 2,5-diphenylcyclohexenylethylamine hydrochloride, as colorless crystals.

UTILITY

The compounds of the invention are highly effective bactericides; they are active against a broad spectrum of bacteria including gram-negative and gram-positive organisms.

The bactericides of the invention are useful in industrial applications such as in adhesives, caulking compounds, cutting oils, paints and the like. They are also useful as bactericides for application to the skin, i.e., they can be incorporated into cosmetics, soaps, and detergents. These utilities will be discussed in greater detail in the following paragraphs.

The bactericides of this invention can be used to control microbiological deterioration of oil-water emulsions. Although oil-water emulsions can contain a wide range of bacteria, the bacteria of the genus Pseudomonas cause the major degradation problems in many instances. The bactericides of this invention are active against a wide variety of bacteria including those of the genus Pseudomonas.

Oil-water emulsions are commonly encountered. For example, wet airplane fuels are often subject to microbiological degradation. In these instances, fouling of fuel lines and corrosion of fuel tanks can occur. The use of the compounds of this invention can reduce or eliminate this problem when added to the fuel in amounts from 0.01 to 1.0 percent.

Another example of an area where oil-water emulsions are widely used is in the machine tool industry. In many grinding and milling operations, cutting oils containing from 2 to 10 percent by weight oil in water are used as both lubricants and cooling agents. These cutting oil systems are open to the air and exposed to contamination which ranges from airborne bacteria to waste organic matter. As the bacterial populations in these oils increase, foul odors develop, thus shortening the useful life of these oil-water emulsions. The bactericides of the invention will alleviate this problem when added to the cutting oils in amounts ranging from 0.01 to 0.1 percent. (When being added to the oils the bactericides should be finely ground and then added to the oil with sufficient agitation to ensure even distribution of the material in the oil-water emulsion.

It is often desirable to grind the active bactericide to obtain a fine particle size. This grinding can be accomplished in ball rills, sand rills, air rills, micropulverizers, and the like.

Bactericides are often added to paints to protect the paint while it is in the can. Thus, the bactericides can be dispersed in a film former solution or suspension in amounts ranging from 0.01 to 1.0 percent. The film former can be any paint, enamels, lacquers or varnish, e.g., latex paints, acrylic paints, alkyd paints, vinyl acrylic paints, alkyd modified acrylics, etc. They are particularly useful with water base paints. The bactericides can be added to the paint by grinding them to a fine particle size and then incorporating them into the solution or suspension with agitation.

The bactericides of the invention can also be used in cosmetics in view of their activity against the bacteria formed on human skin.

The bactericides can be incorporated into cosmetic preparation by thoroughly mixing the finely ground bactericide with the cosmetic emulsion or by thoroughly blending with a dry powder such as a dusting powder. The concentration of the bactericides will vary from 0.01 to 1.0 percent. Examples of cosmetics wherein the bactericides can be employed are liquid deodorant colognes, hand lotions, hand creams, hair dressings, dusting powders, cream hair oil, astringent creams, astringent lotion, and deodorant cream.

Furthermore, many cosmetics are based on oil-water emulsions. These products are subjected to microbiological attack before and during use. Spoilage of the cosmetic before use renders the item unusable while contamination during use can cause the spread of infections. The use of the compounds of this invention can also reduce or eliminate these problems.

The bactericides of the invention can also be used as the bactericidally active ingredient in a large number of soaps and detergents. The use of such soaps and detergents will reduce the bacterial population of the skin.

The bactericides can be incorporated into the soaps and detergents by thoroughly mixing the finely ground compound into the soap or detergent before the final drying stops. The concentration of bactericides should range from 0.01 to 1.0 percent.

The types of soaps which can be so treated include liquid soaps, powdered soaps, and synthetic detergents.

The following examples illustrate the bactericidal activity of the compounds of the invention.

EXAMPLE NO. 7

The test procedure employed is the standard microbiological test tube liquid serial dilution method for determining susceptibility to antibiotics. (Bailey, W. R., and E. G. Scott, 1962. Diagnostic Microbiology, A Textbook for the Isolation and Identification of Pathogenic Microorganisms. The C. V. Mosby Publ. Co., St. Louis, Mo., pp. 250–253.)

The tests were conducted as follows:

Ten mg of the compounds from each of Examples 106 were mixed with 50 ml of sterile, distilled water containing 2.0 ml of dimethylformamide and one drop of Tween 80 surfactant. Appropriate dilutions were made from this solution in sterile distilled water.

Test compound concentrations were made by adding one ml of a diluted solution to 1 ml of sterile, double-strength Difco (Difco Laboratories, Detroit, Michigan) brainheart infusion broth (without PAB) in plugged test tubes.

The final test concentrations of 100 mcg, 50 mcg, 10 mcg, 2 mcg and 0.4 mcg of compound per ml of culture medium were aseptically inoculated with two drops of an overnight broth culture of a test bacterium and incubated at 37°C.

After incubation for 48 hours, the test tubes were observed for signs of growth (turbidity). The lowest compound concentration tested which inhibited the bacterial growth (tubes remained clear) was recorded in the table as the minimal inhibitory concentration (M.I.C.).

The test results are indicated in the following table.

IN ANTIBACTERIAL ACTIVITY IN BRAIN-HEART INFUSION CULTURE BROTH

	M.I.C. (mcg/ml) After 48 Hours at 37°C					
Compound of Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	
Gram-Positive Bacteria						
Bacillus subtilis	10	50	50	100	50	50
Staphylococcus aureus	10	50	50	50	50	50
Streptococcus pyogenes	2	10	10	50	50	10

IN ANTIBACTERIAL ACTIVITY IN BRAIN-HEART INFUSION CULTURE BROTH

	M.I.C. (mcg/ml) After 48 Hours at 37°C					
Compound of	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6
Gram-Negative Bacteria						
Salmonella typhimurium	10	50	50	50	50	50
Escherichia coli	10	50	50	100	100	50
Pseudomonas aeruginosa	10	>100	>100	>100	>100	>100
Proteus vulgaris	50	>100	>100	>100	>100	>100
Klebsiella aerobacter	10	100	100	>100	>100	100
Serratia marcescens	50	>100	>100	>100	>100	100
Aerobacter cloacae	10	50	50	50	50	50

EXAMPLE NO. 8

A standard cutting oil, Sun Oil's "SECO" oil, is diluted with water to give 950 parts of a 3 percent by weight oil-water emulsion. To this emulsion is added 50 parts of a rancid oil. The mixture is stirred and allowed to sit for 4 to 6 weeks. Samples are taken and a colony count is made of the bacteria present in the emulsion by the standard quantitative plate count method. The counts obtained are indicated in the following Table.

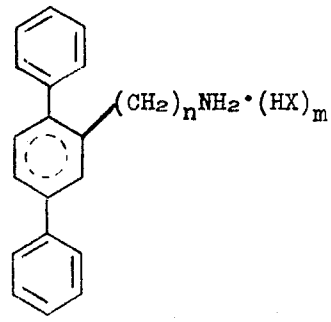
Some of the samples are then treated with the indicated amounts of 2,5-diphenylcyclohexenylmethylamine hydrochloride, the compound having been finely ground with glass beads in a rill. Colony counts are then taken at the times indicated and the results are also indicated in the Table.

TABLE

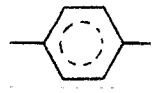
Sample	Initial Count	Amt. of Bacteri-cide added	Elapsed Time until sample drawn for second count	Second Count
A	37 MM/ml	0.2 %	1 hour	0
B	3.5 MM/ml	0.02%	2 days	0.5 MM/ml

We claim:

1. A compound of the formula



wherein



is selected from the group consisting of cyclohexylene, cyclohexenylene, cyclohexadienylene and phenylene; *n* is 1 or 2; *m* is 0, ½ or 1; and X is halogen, sulfate or bisulfate.

2. The compound of claim **1** wherein *n* is 1.

3. 2,5-Diphenylcyclohexenylmethylamine hydrochloride.

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