

UNITED STATES PATENT OFFICE

2,569,408

QUATERNARY SALTS—ALKYLBENZYL
ALKYL DIMETHYL AMMONIUM HAL-
IDES

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No Drawing. Application June 29, 1949,
Serial No. 102,144

4 Claims. (Cl. 260—567.6)

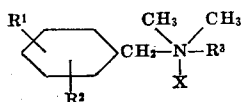
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This invention deals with alkylbenzyl alkyl dimethyl ammonium halides which contain alkyl substituents of six to ten carbon atoms and which are characterized by their surface-activity and by their efficiency as bactericides and fungicides.

It has been demonstrated that the effectiveness of surface-active compounds depends upon a balance of hydrophobic and hydrophilic portions and upon the orientation of molecules resulting in part from this balance. Molecules which contain a number of hydrophobic groups or hydrophilic groups scattered about the molecular structure have not in general proved to be useful capillary-active materials. Thus, it has been considered desirable to use a single large hydrophobic group in a molecule to give definite orientation thereto. In the case of quaternary ammonium salts, to be more specific, the most useful surface-active compound and those which have bactericidal value have had a single aliphatic hydrocarbon group of 12 to 18 carbon atoms attached to the quaternary nitrogen and have had the other valences of the nitrogen satisfied with the smallest practical groups. Recently we found that a long chained aliphatic hydrocarbon group can be replaced with a single alkylbenzyl group containing a total of 15 to 26 carbon atoms. Both these types of compounds fulfill the classical requirements for a useful and satisfactory surface-active structure. They have, indeed, been found highly useful in applications in which this activity plays a role.

In contrast to the indications of the art as it has thus far developed, we have now discovered a class of quaternary ammonium salts which are capillary-active and which have high bactericidal and fungicidal activities when the quaternary nitrogen carries both an alkyl group of moderate size and an alkyl benzyl group also of moderate size, the sizes of both groups being as defined below. Unexpectedly and contrary to a logical development of the usual theories of capillary activity and chemical structure, this new class of compounds furnishes far more effective bactericides and fungicides than those types wherein the carbon atoms are concentrated in a single hydrophobic group.

These new compounds have the general structure

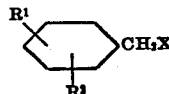


where R¹ is an alkyl group of six to ten carbon atoms, R³ is an alkyl group of six to ten carbon

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atoms, R² is hydrogen or methyl, and X is chlorine or bromine. The size of the substituent R groups, however, is further restricted by the requirement that the sum of the number of carbon atoms in R¹, R², and R³ must equal at least 15 and not exceed 19. There is thus a rather narrow range within which particularly effective and useful compounds are available. Effectiveness as measured by bactericidal and fungicidal actions falls off as the number of carbon atoms in either R¹ or R³ deviates from the above-prescribed values.

The defined compounds can be prepared by reacting together an alkylbenzyl halide,



20 and an alkyldimethylamine,



25 Temperatures of 20° to 120° C. are useful for performing this reaction. The two components may be combined directly or, preferably, they may be reacted in an inert organic solvent. Useful solvents include hydrocarbons, such as benzene, toluene, and xylene, alcohols such as isopropanol, and miscellaneous solvents such as acetonitrile, formamide, and nitromethane.

The preparation of alkylbenzyl halides of the required size requires the use of somewhat special conditions in order to secure monohalomethylation and at the same time avoid formation of resinous materials. The necessary conditions are set forth in our application Serial No. 28,274, filed May 20, 1948, now abandoned. As there shown, an alkylbenzene or an alkyltoluene in which the alkyl groups contain eight or more carbon atoms is halomethylated by reacting it with anhydrous formaldehyde and hydrogen chloride (or hydrogen bromide) in the presence of a catalyst mixture formed by mixing one molecular proportion of zinc chloride with 1.5 to 8 molecular proportions of an aliphatic monocarboxylic acid of one to three carbon atoms, such as formic, acetic, chloroacetic, or propionic. Acid anhydrides are equivalent to the acids and may be used in place thereof or in admixture therewith. Formaldehyde may be used as a gas or as a reversible polymer. The equivalent of formaldehyde and hydrogen chloride or bromide is obtained by use of a halomethyl ether. For one mole of an alkyl-

benzene or the equivalent alkyltoluene from one to 2.5, and preferably 1.5 to 2.5, moles of formaldehyde are taken along with 0.75 to 2.5 molecular proportions of zinc chloride in association with a proportion of monocarboxylic acid defined above. The halomethylation with a hydrogen halide is effected at 50° to 100° C.

This method gives good yields with alkyl groups of at least eight carbon atoms. Yields improve as the number of carbon atoms increases from eight to twelve. On the other hand, they decrease as the number of carbon atoms becomes smaller. Thus, with hexyl- or heptyl-benzenes or -toluenes there is desirably some adjustment in this method. Additional formic, acetic, or propionic acid, or the equivalent, which serves as a diluent, should be used and/or lower temperatures if good yields are to be obtained. In any case the conditions of halomethylation should be so selected and so adjusted that the main reaction constitutes the introduction of one halomethyl group in an alkylbenzene or alkyltoluene molecule and at the same time polyhalomethylation is avoided. Under these conditions resinous by-products are not formed.

For the above alkylbenzenes and alkyltoluenes there are used those in which the alkyl group contains six to ten carbon atoms. The exact form of the alkyl group does not appear to be of great import. It may be of straight or branched chain structure; it may be primary, secondary, or tertiary. The relative position of such alkyl group and the methyl group in the alkyltoluenes is unimportant. It should be stated, however, that the alkylbenzenes are preferable to the alkyltoluenes. The relative position of the alkyl group to the methylene group of the halomethylated product and the final quaternary salt has not been found to be of particular importance.

The alkylated hydrocarbons are prepared by known methods. For example, an acyl halide may be reacted with benzene or toluene and the acyl group thus introduced be then reduced. By other procedures olefinic hydrocarbons of the required size are reacted with benzene or toluene. The desired alkyl groups vary in size from hexyl to decyl. There may thus be used the various hexylbenzenes, hexyltoluenes, heptylbenzenes, heptyltoluenes, octylbenzenes, octyltoluenes, nonylbenzenes, nonyltoluenes, decylbenzenes and decyltoluenes. For economic reasons various secondary and tertiary alkyl groups are particularly desirable in the above compounds. Alkylbenzenes having alkyl groups of six to nine carbon atoms are obtained from readily available starting materials.

The following preparation of sec.-octylbenzyl chloride is given to illustrate a good method of preparation of an alkylbenzyl chloride where the alkyl group is of such weight that methods of the art are not satisfactory. A mixture of 95 parts of sec.-octylbenzene, 30 parts of paraformaldehyde, 54 parts of zinc chloride, and 120 parts of glacial acetic acid was stirred at 50° C. while hydrogen chloride gas was passed into the mixture for two hours. The upper layer was separated, washed with hot water, with a 10% sodium bicarbonate solution, and with water again, dried over anhydrous sodium sulfate, and distilled. After a forerun of 30 parts of octylbenzene there was obtained a fraction of 71 parts of octylbenzyl chloride, distilling at 119°-121° C./1 mm. This was a practically quantitative recovery. The product was pure and ready for reaction with an alkyl-

The alkyl dimethylamines which may be used include hexyldimethylamine, 2-ethylbutyldimethylamine, heptyldimethylamine, 2-ethylhexyldimethylamine, octyldimethylamine, nonyldimethylamine, decyldimethylamine, and the various isomers thereof. As is known, these amines are available through the reaction of alcohols or alkyl halides and dimethylamine.

Further details of methods of preparation will be found in the following illustrative examples.

EXAMPLE 1

Hexylbenzene, prepared by the alkylation of benzene with propylene dimer, was mixed in an amount of 60 parts by weight with 25 parts of zinc chloride and 25 parts of acetic acid at 50°-55° C., and 40 parts of dichloromethyl ether was added thereto over a period of one hour. The reaction mixture was held at 55°-60° C. for an hour. The mixture was then cooled and the upper layer, which had formed, was separated. This was washed with water and sodium bicarbonate solution and then distilled under reduced pressure. The fraction collected at 120°-130° C./0.2 mm. corresponded in composition to hexylbenzyl chloride. It was chiefly p-(1,3-dimethylbutyl) benzyl chloride along with some isomers.

Decyldimethylamine was prepared by reacting n-decanol and dimethylamine at 260° C. on a copper chromite catalyst under hydrogen pressure.

There were mixed 8.05 parts of hexylbenzyl chloride and 7 parts of decyldimethylamine in 20 parts of acetonitrile. The mixture was heated under reflux for eight hours. The solvent was then distilled off and the residue heated under reduced pressure. A waxy, light yellow solid was obtained which corresponded in composition to hexylbenzyl decyl dimethyl ammonium chloride. It had an ionizable chlorine content of 9.05%, compared to the theoretical content of 9.05%. This product was tested for its bactericidal value and was found to be very effective. It gave a phenol coefficient against *Staphylococcus aureus* of 710 and against *Salmonella typhosa* of 500. Aqueous solutions of this compound have very low surface tensions. Thus, the 0.5% to 1% solutions give values of 29.1 dynes/cm. at about 25° C.

EXAMPLE 2

Commercial 3-heptanol was dehydrated at 400° C. on an alumina catalyst and the heptene therefrom redistilled. A mixture was made from 125 parts by weight of this olefin, 198 parts of benzene, and 196 parts of sulfuric acid at 5° C. The mixture was stirred for three hours, allowed to form layers, and separated. The organic layer was washed with water and a little soda ash solution, dried, and distilled under reduced pressure. There were thus obtained 167 parts of heptylbenzene.

A mixture was made from 160 parts of this product, 90 parts of anhydrous zinc chloride, and 138 parts of glacial acetic acid, and 106 parts of dichloromethyl ether were added thereto while the temperature of the reaction mixture was held at 60° C. and then maintained at this temperature for five hours. The mixture was cooled and permitted to form layers, which were separated. The product layer was washed, dried, and fractionally distilled. A fraction was obtained at 127°-132° C./2 mm. which corresponded in composition to heptylbenzyl chloride.

A nonyldimethylamine was prepared from a

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nonyl alcohol, 3,5,5-trimethylhexanol, and dimethylamine.

There were mixed 14 parts of heptylbenzyl chloride and 10.8 parts of nonyldimethylamine in 50 parts of benzene. The mixture was heated for about one-half hour. The benzene was distilled off under reduced pressure, leaving 24 parts of a soaplike solid, which corresponded in composition to heptylbenzyl nonyl dimethyl ammonium chloride.

A solution of this salt was evaluated by the F. D. A. method for determining phenol coefficients. A value of 500 was obtained against *Staphylococcus aureus* and of 330 against *Salmonella typhosa*.

Essentially the same phenol coefficients are found for a heptylbenzyl nonyl dimethyl ammonium chloride in which the heptyl group is 4,4-dimethylpentyl.

EXAMPLE 3

Diisobutyl carbinol was dehydrated by dripping it onto an alumina catalyst at 400° C. The vapors were condensed and distilled to yield 2,6-dimethyl-3-heptene. To a stirred mixture of 159 parts of benzene and 147 parts of sulfuric acid there was added 135 parts of this nonene with the temperature at 5° C. at the start of the reaction and held between 5° and 10° C. during the addition. The reaction mixture was stirred for three hours at room temperature, cooled, allowed to form layers, and separated. After the upper layer had been washed and dried, it was distilled. The fraction obtained at 102°-106° C./3 mm. corresponded in composition to nonylbenzene.

There were mixed 80 parts of this product, 40 parts of anhydrous zinc chloride, and 60 parts of glacial acetic acid. With the temperature of this mixture at about 25° C. there was added 45 parts of dichloromethyl ether. This mixture was stirred and heated at 70° C. for three hours, then cooled, and separated. The upper layer was washed with water and with sodium bicarbonate solution, dried over sodium sulfate, and distilled at low pressure. The fraction taken at 141°-142° C./2 mm. corresponded in composition to nonylbenzyl chloride. It contained 14.4% of chlorine while the theoretical chlorine content is 14.1%.

A solution of 90 parts of this nonylbenzyl chloride, (1-isopropyl-4-methylpentyl) benzyl chloride, and 51 parts of heptyldimethylamine in 250 parts of benzene was heated under reflux for two hours. The solvent was removed under reduced pressure to yield 139 parts of a waxy solid, nonylbenzyl heptyl dimethyl ammonium chloride.

Evaluation of this product made against *Staphylococcus aureus* and *Salmonella typhosa* gave phenol coefficients of 830 and 470 respectively.

EXAMPLE 4

There were mixed 79 parts of the above nonylbenzyl chloride and 49 parts of 2-ethylhexyldimethylamine in 250 parts of a close-cut aromatic solvent. The mixture was heated on a steam bath for twenty minutes. The solvent was removed under reduced pressure. There remained 125 parts of a colorless, soft, waxy solid which approximately corresponded in composition to nonylbenzyl 2-ethylhexyl dimethyl ammonium chloride. The chlorine analysis of this product showed a chlorine content of 8.1%, compared to a theoretical value of 8.6%.

Phenol coefficients for this product were found to be 460 against *Staphylococcus aureus* and 330 against *Salmonella typhosa*.

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EXAMPLE 5

There were reacted in a conventional manner one mole of mixed octenes boiling at 123°-124° C. and one mole of benzene at 0° to 10° C. with anhydrous hydrogen fluoride serving as catalyst. The mixture was stirred for two hours and dropped into an ice bath. The organic layer was separated, washed with water and a 5% sodium bicarbonate solution, dried over soluble anhydrite, and distilled, the fraction being collected which corresponded to octylbenzene in composition.

This was converted to octylbenzyl chloride by the same method detailed above. The mixture of octylbenzene, zinc chloride, and acetic acid was reacted with chloromethyl ether at 50°-60° C. for four hours. The mixture was then cooled and separated. After the upper layer had been washed with water and sodium bicarbonate solution, it was distilled to give a fraction corresponding in composition to octylbenzyl chloride.

There were mixed 23.8 parts of this product, 17.1 parts of nonyldimethylamine (from 3,5,5-trimethylhexanol and dimethylamine), and 55 parts of acetonitrile. The mixture was heated for 16 hours under reflux. When the reaction mixture was cooled, crystals formed. They were separated by filtration and dried in vacuo. The dried product corresponded in composition to octylbenzyl nonyl dimethyl ammonium chloride.

This product was found to have phenol coefficients of 710 and 575 against *Staphylococcus aureus* and *Salmonella typhosa* respectively. The surface tension of a 1% aqueous solution was 29.8 dynes/cm. at 25° C.

Bactericidal and bacteriostatic values were determined from the greatest dilutions at which bactericidal and bacteriostatic effects were positively indicated with various organisms, both Gram-positive and Gram-negative. A successive dilution method was used in which trypticase-soy broth was utilized. One per cent solutions of the products under test were diluted with broth and the various dilutions autoclaved for ten minutes at 10 to 12 pounds pressure. They were cooled and inoculated with a 4 mm. loopful of a culture of a test organism. Incubation was carried out at 37° C. for 24 hours. The highest dilution showing no growth gave the dilution for bacteriostatic action. After an additional 24 hours of incubation at 37° C. subcultures were made by transferring three loopfuls from cultures showing no growth to fresh broth. The subcultures were incubated 48 hours at 37° C. The highest dilution showing no growth was the end-point for bactericidal action.

Data thus determined for octylbenzyl nonyl dimethyl ammonium chloride as a typical compound of this invention are shown in the table where Bs is the bacteriostatic dilution and Bc the bactericidal dilution.

Table

Organism	Gram-type	Effective Dilutions/1000	
		Bs	Bc
<i>S. aureus</i>	+	4,000	320
<i>S. pyogenes</i>	+	4,000	4,000
<i>S. fecalis</i>	+	1,000	320
<i>N. catarrhalis</i>	-	4,000	4,000
<i>S. typhosa</i>	-	160	160
<i>Ps. aeruginosa</i>	-	40	80
<i>P. vulgaris</i>	-	20	10
<i>C. welchii</i>	-	1,000	80

It will be noted that against the commonly used test organism *Staphylococcus aureus* and also

against some other organisms bacteriostatic effects were obtained at dilutions of 1 to 4,000,000. Even with very resistant Gram-negative organisms dilutions of 1 to 20,000 and 1 to 40,000 were effective bacteriostatically.

EXAMPLE 6

There was prepared decylbenzene by dehydrating n-decanol on alumina at 400° C. and reacting the 1-decene thus obtained with benzene with sulfuric acid as a catalyst. There was obtained 2-decylbenzene. This was reacted with chloromethyl ether under the influence of zinc chloride and acetic acid in accordance with details given above. There was thus obtained p-(2-decyl)-benzyl chloride.

There were mixed 95.5 parts of this chloride and 56 parts of 2-ethylhexyldimethylamine in 250 parts of benzene. The mixture was heated under reflux for about an hour and the benzene distilled therefrom under reduced pressure. The residue was a soft, waxy solid which corresponded in composition to decylbenzyl 2-ethylhexyl dimethyl ammonium chloride.

Phenol coefficients of 500 and 330 were determined therefor in tests with *Staphylococcus aureus* and *Salmonella typhosa* respectively.

A quaternary ammonium halide of almost the same potency is obtained when octylmethylbenzyl chloride is reacted with decyldimethylamine.

EXAMPLE 7

A solution of 30.7 parts of decylbenzyl chloride and 17.1 parts of a nonyldimethylamine in 50 parts of nitromethane were heated at 70°-100° C. for four hours and the solvent stripped therefrom. The residue was taken up in benzene and crystallized therefrom. The crystals were fairly pure decylbenzyl nonyl dimethyl ammonium chloride. Additional, only slightly less pure salt was obtained as a residue.

This compound was found to have phenol coefficients of 250 against *Salmonella typhosa* and of 765 against *Staphylococcus aureus*.

The surface tension of solutions of 0.5% to 1% of this compound in water was less than 30 dynes/cm.

EXAMPLE 8

In the same way there was prepared nonylmethylbenzyl nonyl dimethyl ammonium chloride, the nonyl groups being 3,5,5-trimethylhexyl. The phenol coefficients found for this product were 235 against *Salmonella typhosa* and 535 against *Staphylococcus aureus*.

The preparation was repeated by reacting p-(3,5,5-trimethylhexyl)benzyl chloride and (3,5,5-trimethylhexyl)dimethylamine in molecularly equivalent amounts. The product, a nonylbenzyl nonyl dimethyl ammonium chloride, gave phenol coefficients of 385 against *Salmonella typhosa* and of 1400 against *Staphylococcus aureus*.

EXAMPLE 9

To a mixture of 46 parts of sec.-octylbenzene, 17 parts of zinc chloride, and 40 parts of glacial acetic acid there was added dropwise 50 parts of bisbromomethyl ether. The mixture was stirred and maintained at 70° C. during the mixing and thereafter for two hours. The mixture was allowed to stand. Layers developed and were separated. The upper layer was washed with hot water, a 10% sodium bicarbonate solution, and again with water, dried, and distilled. At

155°-174° C./2 mm. there was obtained a fraction which corresponded in composition with that of octylbenzyl bromide.

There were dissolved in 200 parts by weight of acetonitrile 28.3 parts of octylbenzyl bromide and then 17.1 parts of nonyldimethylamine. A precipitate formed at once. This was dissolved when the mixture was heated. The mixture was then cooled to 0° C. and the precipitate which formed separated. There was thus obtained octylbenzyl nonyl dimethyl ammonium bromide as a crystalline, colorless salt.

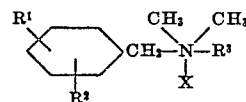
Against *Staphylococcus aureus* it had a phenol coefficient of 1750; against *Salmonella typhosa* it had a phenol coefficient of 500. The surface tension of a 1% solution of this compound was 25.5 dynes/cm. at about 25° C.

Thus, within the range of alkyl groups having six to ten carbon atoms when the total of the carbon atoms in the alkylbenzyl and in the major alkyl N-substituents is not over 19, the alkylbenzyl alkyl dimethyl ammonium halides are surface-active compounds which have high bactericidal value. Increase or decrease in the size of the critical groups is accompanied by a considerable change in such value. For instance, amylbenzyl octyl dimethyl ammonium chloride has a phenol coefficient against *Salmonella typhosa* of only about 60.

These compounds all inhibit germination of spores of such fungi as *Macrosporium sarcinaeforme* and *Sclerotinia fruticola* at considerable dilution.

We claim:

1. As new chemical substances, compounds of the formula



wherein X is a halogen from the class consisting of chlorine and bromine, R¹ is an alkyl group of six to ten carbon atoms, R² is a member of the class consisting of hydrogen and the methyl group and R³ is an alkyl group of six to ten carbon atoms, the size of the groups R¹, R² and R³ being so chosen that the sum of carbon atoms therein is 15 to 19.

2. As a new compound, octylbenzyl nonyl dimethyl ammonium bromide.

3. As a new compound, nonylbenzyl nonyl dimethyl ammonium chloride.

4. As a new compound, octylbenzyl nonyl dimethyl ammonium chloride.

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