

Aug. 10, 1948.

R. S. SHELTON ET AL
SUBSTITUTED PYRIDINIUM AND
PIPERIDINIUM COMPOUNDS

2,446,792

Filed Aug. 28, 1943

3 Sheets-Sheet 1

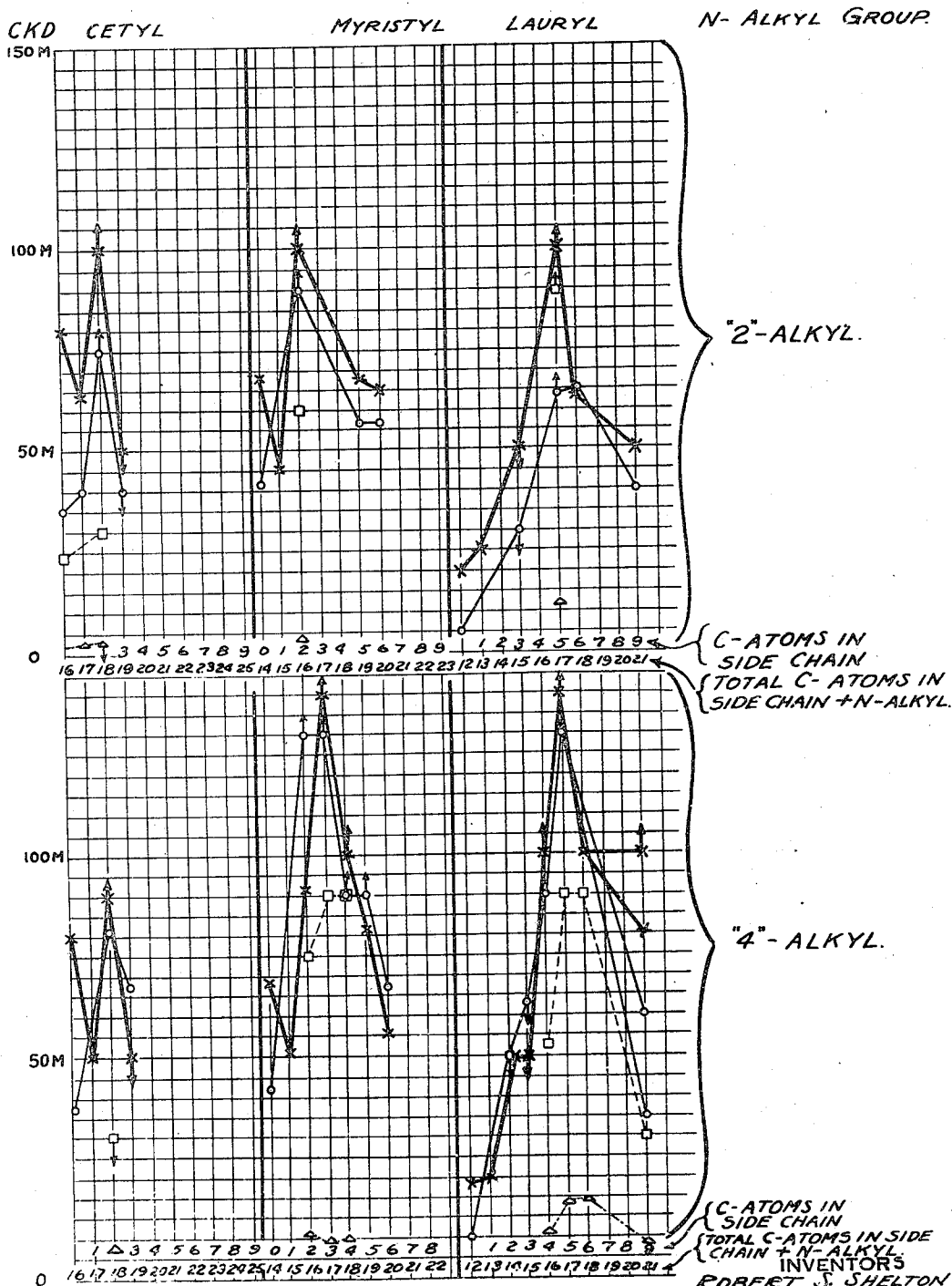


Fig. 1

BY
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ATTORNEY

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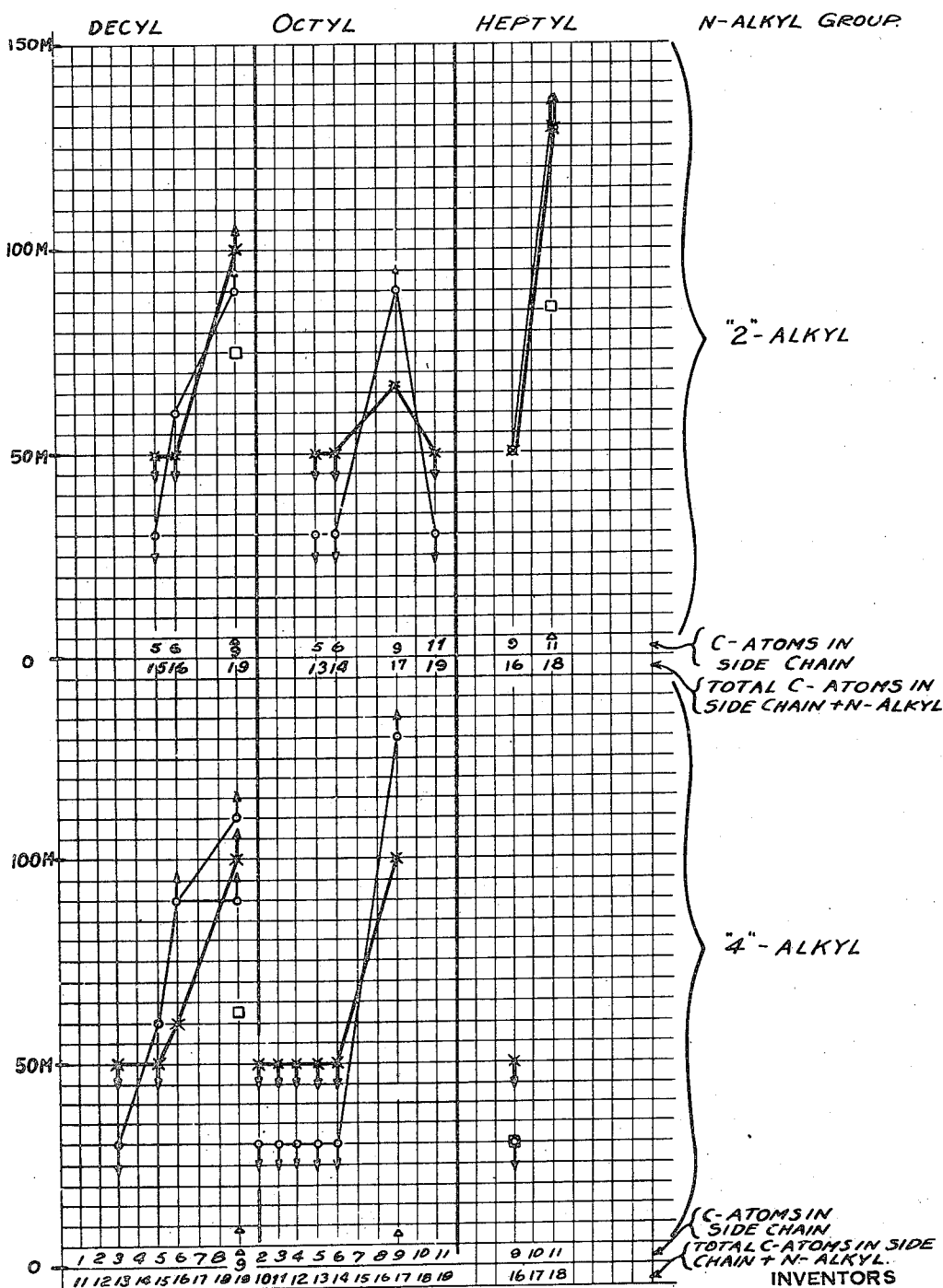


Fig. 2

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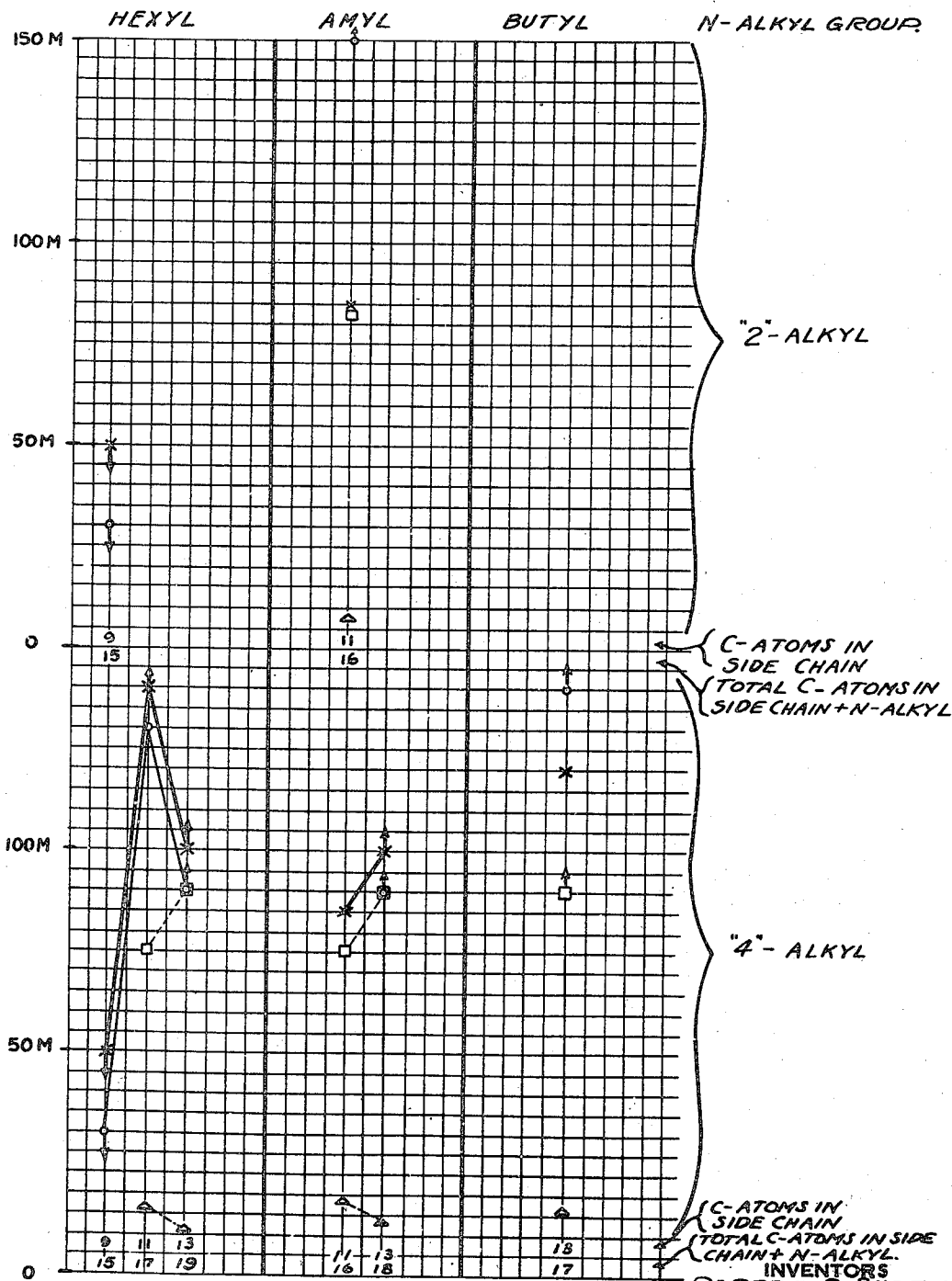


Fig. 3

UNITED STATES PATENT OFFICE

2,446,792

SUBSTITUTED PYRIDINIUM AND PIPERIDINIUM COMPOUNDS

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Application August 28, 1943, Serial No. 500,340

21 Claims. (Cl. 260—295)

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This invention relates to compositions of matter for counteracting micro-organisms, generally referred to as "germs," including bacteria, fungi, and the like; and especially to compositions suitable for general use on inanimate objects as well as in treatment of wounds, skin and mucous surfaces, etc. Although the compositions of our invention will most often be used as germicides, i. e. for killing of such micro-organisms, they may also be used to inhibit growth of such organisms ("bacteriostatic" action) or to render germs more or less innocuous by a partial or complete nullification of their harmful effects or by inhibition of their normal activity which produces the harmful effects. We refer to these various related uses generally, as "germ-counteracting."

Prior to our present invention it had been known that quaternary ammonium compounds of the type having one higher molecular aliphatic constituent on the ammonium nitrogen exhibit germicidal and bacteriostatic effects. In the prior patent of one of us, No. 2,295,504, it was disclosed that within this broad class of compounds extraordinary activity was exhibited by those having one higher molecular constituent on the ammonium nitrogen of 16 carbon atoms. Surprisingly, as there shown, although a change of two or more in the number of carbon atoms in the high molecular weight constituent resulted in very significant changes in the activity of the compound no similar correlation was found between the size and nature of the low molecular weight constituent and the activity. Thus, such different compounds as cetyl trimethyl ammonium salts, cetyl tributyl ammonium salts, cetyl methyl piperidinium salts and cetyl pyridinium salts were all strikingly superior to the lauryl or stearyl homologues corresponding to any of these.

This generalization remains true with the substitution of a methyl group or groups on the pyridinium or piperidinium nucleus; but we have now discovered that surprisingly, when the length of the side chain on such a heterocyclic nucleus including quaternary ammonium nitrogen is increased, it begins to partake of and to modify the critical nature of the higher molecular constituent. The cetyl compounds maintain their relatively higher activity up to the ethyl substitutions on a carbon atom of the heterocyclic nucleus; and the cetyl pyridinium compounds are made most active by such ethyl substitution. Beginning with the ethyl substitution on the

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N-alkyl compounds of the type mentioned, and becoming more evident with side chains of increasing lengths, two effects are introduced: first the peaks of activity depend not upon the high molecular weight substituent alone, but upon the sum of the carbon atoms in the high molecular weight substituent and in the side chain having at least 2 carbon atoms; and secondly, the peak activity bears a sharply critical relation to this sum of the carbon atoms in the higher molecular weight group on the nitrogen and the lower molecular weight side chain on the heterocyclic nucleus, this peak appearing in the range from 16 to 18 carbon atoms. A minor anomaly appears when the respective substituent groups approach each other in number of C-atoms, the peak in such case usually appearing at 18 or 19 C-atoms, or in general in the range 17-19 C-atoms. Even in this case, however, highly active compounds below the peak activity occur in the range 16-18.

The high molecular weight radical attached to the ammonium nitrogen atom may be alkyl, alkenyl or acylated derivatives of alkyl and alkenyl radicals, e. g. of the $-\text{COOR}$, $-\text{OCOR}$, $-\text{CONHR}$ types, wherein R is alkyl or alkenyl.

Additional surprising advantages are found for the compounds of this new type. In the first place, whereas the quaternary ammonium germicides generally have shown a substantial reduction of germicidal activity at temperatures substantially below body temperature, such as to require much higher concentration for germicidal solutions to be used on inanimate objects, such compounds when they have an alkyl side chain of several carbon atoms in length attached to one of the carbon atoms of the heterocyclic nucleus, not only reach a peak activity when the sum of the carbon atoms in said side chain plus those of the radical attached to the ammonium nitrogen is in the range stated, but this activity is better maintained at lower temperatures.

Moreover, in this range of anomalous activity, the activity of the compounds as against Gram-negative organisms (represented for example, by *E. typhosa*) rapidly comes abreast of the activity as against the Gram-positive organisms (represented by *Staph. aureus*); although with quaternary ammonium compounds in general it is substantially lower. At the peak activities the compounds of the present invention are usually at

least as effective against the Gram-negative types as against the Gram-positive organisms and often are more active. Inasmuch as the organisms of the Gram-negative type are often considered to be of greater importance in the disinfection of inanimate objects, the relatively high activity as against these organisms, and more especially the equally high activity against both types of organisms, as well as the maintained activity at lower temperatures, are of great practical importance. Reference is also made to applicants' copending applications Ser. No. 603,269 and Ser. No. 645,482, both containing related subject matter.

The toxicity of these compounds of our present invention is not increased as the activity against micro-organisms is increased. Thus there is a striking and extraordinary increase in the selective action against such micro-organisms in the presence of living tissues. As examples of this: N-lauryl 4-n-amyl pyridinium chloride injected intraperitoneally into mice, 2.5% aqueous solution 0.3 cc. per kg. of body weight killed only 20% of the animals. The same dosage with N-n-amyl-4-n-tridecyl pyridinium bromide and with N-n-butyl 4-n-tridecyl pyridinium bromide resulted in no deaths. All of these compounds show much lower toxicity with intravenous injection, and are even less toxic upon oral administration.

Due to the extraordinarily high activity of these compounds against pathogenic organisms at relatively low temperatures and to their low toxicity to the human organism, higher plants and animals, these compounds have been found particularly valuable for sterilization of drinking water, leafy vegetables and other foods and beverages which are likely to carry infection and are to be drunk or eaten without further cooking.

Likewise, due to the properties mentioned above and to the hygroscopic nature of these compounds, they are particularly advantageous for hospital and sick room sanitation. By washing room surfaces and particularly bed linens and bed clothing with a solution of these compounds, the surfaces are rendered antiseptic and by allowing a film of such solution to remain on these surfaces, airborne germs which may accumulate thereon are rendered innocuous and the spread of infection by stirring up such germs during cleaning, bed-making, etc. can be largely avoided. Since these compounds are also soluble in oil and are powerful emulsifying agents, they may be applied for this purpose in oil emulsion, the oil

serving more effectively to catch and hold dust particles.

These same properties make the compounds of our invention very good for preservation of such substances as fruits, vegetables, other foods, clothing, shoes, wood and various organic substances against attack by micro-organisms, including insect larvae.

In the following table we have shown a number of examples of our invention. A halogen analysis is included in this table since, in general, a variation from the calculated composition indicates the presence of tertiary amine salts or other relatively inactive substances which, if calculated as a quaternary ammonium compound, would, of course, reduce the apparent activity. It will be observed from this table that, in general, and except where impurity is noted under "Remarks," the observed percentage of halogens conforms within the limits of high purity and experimental error with the calculated percentage.

For purposes of comparison it may be stated that the homologous compounds beyond the specified range of our invention show much lower activities, their critical killing dilutions, in general, dropping to less than about 1:30,000 for *E. typhosa* and 1:50,000 for *Staphylococcus aureus*, at 37° C. When the sum of the carbon atoms in the high molecular weight substituent on the nitrogen atom and in the side chain of two or more carbon atoms on the heterocyclic nucleus amounts to from 16 to 18 carbon atoms, the activity (expressed as C. K. D.) is significantly increased to a peak ordinarily 50% or 100% or more higher than the activity of such compounds outside of the critical range.

It will also be observed that, whereas in general germicidal effectiveness is substantially reduced in the presence of 10% serum at room temperature, in several cases the compounds having the peak activity also have surprising immunity to the presence of serum.

Although the tests represented by this data have been carried out under carefully controlled conditions such that the data is believed to be adequate for forming comparisons and conclusions, it should be remembered that although the tests are made with standardized strains of the organisms, they still are living organisms which may vary from test to test in their resistance to germicidal compounds and also that the presence or absence of impurities may vary to some extent the exact figures obtained:

Compound	C. K. D. <i>Staph. Aur.</i> at 37° C. no serum	C. K. D. <i>Eber, Typhosa</i>			Melting Point, °C.	Water Solubility, 25°	Halogen Analysis		Remarks
		37° no serum	20° no serum	20° 10 per cent serum			obs. per cent	calc. per cent	
N-Alkyl Amyl Pyridinium: N-Lauryl 2-n-amylpyr. Br.....	1:100M+	-----	1:90M+	1:12M	25-30	1:5	21.3	20.05	hygroscopic; 94% pure.
N-Lauryl 4-n-amylpyr. Br.....	1:140M+	1:130M+	1:90M	1:13,500	85-87	1:35	20.0	20.05	hygroscopic.
N-Lauryl 4-n-amylpyr. Cl.....	1:130M+	1:130M+	1:90M+	1:18M+	49-51	1:30	9.97	9.98	Do.
N-Alkyl Hexylpyridinium: N-Lauryl 2-hexylpyr. Br.....	1:69M	1:70M	-----	-----	76-78	1:5	19.33	19.38	Do.
N-Decyl 4-n-hexylpyr. Cl.....	1:60M	1:90M+	-----	-----	-----	1:5	20.7	20.8	hygroscopic; see other samples.
N-Lauryl 4-n-hexylpyr. Br.....	1:100M+	-----	1:90M	1:14,250	99-101	1:15	19.25	19.40	hygroscopic.
N-Alkyl Ethylpyridinium: N-Cetyl 2-ethylpyr. Br.....	1:100M*+	1:75M+	1:30M	1:3M-	88-90	1:5	19.5	19.4	Do.
N-Myristyl 2-ethylpyr. Br.....	1:100M+	1:90M+	1:60M	1:3750	70-72	1:5	20.35	20.30	Do.
N-Myristyl 4-ethylpyr. Br.....	1:92M	1:130M+	1:75M	1:6M	50-52	1:5	20.3	20.3	Do.
N-Cetyl 4-ethylpyr. Br.....	1:90M+	1:82M	1:30M-	1:3M	67-69	1:25	19.3	19.4	Do.
N-Cetyl 4-ethylpyr. Cl.....	1:100M+	1:78½M	1:30M	1:3M-	67-70	1:5	9.54	9.63	Do.
N-Alkyl Propyl pyridinium: N- Myristyl 4-n-propylpyr. Br.....	1:140M+	1:130M+	1:90M	1:4500	64-67	1:5	19.9	20.1	Do.
N-Alkyl Butyl Pyridinium: N-Lauryl 4-n-butylpyr. Br.....	1:100M+	1:90M	1:52M	1:6M	58-60	1:5	20.7	20.8	very hygroscopic.
N-Myristyl 4-n-butylpyr. Br.....	1:100M+	1:90M+	1:90M+	1:4500	75-77	1:5	19.0	19.0	hygroscopic; a hemi- hydrate.

Compound	C. K. D. Staph. Aur. at 37° C. no serum	C. K. D. Eber. Typhosa			Melting Point, °C.	Water Solubility, 25°	Halogen Analysis		Remarks
		37° no serum	20° no serum	20° 10 per cent serum			obs. per cent	calc. per cent	
N-Alkyl Nonyl pyridinium: N-n-Octyl-2-(2-methyloctyl) pyr. Br.	1:67M	1:90M			65-67	1:5	19.9	20.0	hygroscopic.
N-n-Decyl-2-(2-methyloctyl) pyr. Br.	1:100M+	1:90M+	1:75M	1:3750	65-67	1:30	18.8	18.7	gels at 1:5 conc.; hygroscopic.
N-n-Octyl 4-(2-methyloctyl) pyr. Br.	1:100M	1:130M+	1:42½M	1:7½M	25	1:300	20.2	20.1	hygroscopic.
N-n-Decyl 4-(2-methyloctyl) pyr. Br.	1:100M+	1:90M+		1:9750	25	1:600	18.8	18.75	Do.
N-n-Lauryl 4-(2-methyloctyl) pyr. Br.	1:30M	1:35M		1:3M	25	1:1400	17.55	17.6	Do.
N-n-Decyl 4-(5-nonyl) pyr. Br.	1:100M+	1:110M	1:62½M	1:3M	oil	1:600	18.7	18.7	
N-lauryl 4-(5-nonyl) pyr. Br.	1:100M+	1:60M	1:30M		oil	1:2M	17.6	17.6	
N-n-Decyl 4-(n-nonyl) pyr. Br.	1:100M+	1:90M+	1:90M+	1:12M		1:600			
N-Alkyl Undecyl pyridinium: N-n-Amyl 2-n-undecylpyr. Br.	1:85M	1:150M+	1:61M-1:82M	1:7½M	55-58	1:5	21.2	20.8	91% pure; hygro- scopic.
N-n-Heptyl 2-n-undecylpyr. Br.	1:130M+	1:130M+	1:86M	1:4½M	65-68	1:5	19.7	19.4	95% pure.
N-n-Amyl 4-n-undecylpyr. Br.	1:85M		1:75M	1:13½M	62-64	1:5	21.1	20.3	94% pure; hygro- scopic.
N-n-Hexyl 4-n-undecylpyr. Br.	1:140M+	1:130M	1:75M	1:12M	81-83	1:25	19.95	20.05	pure, very hygro- scopic.
N-Alkyl Tridecyl pyridinium: N-n-Butyl 4-n-tridecylpyr. Br.	1:120M	1:140M+	1:90M+	1:11M	64-66	1:5	19.95	20.05	slightly hygroscopic.
N-n-Amyl 4-n-tridecylpyr. Br.	1:100M+	1:90M+	1:90M+	1:9M	43-45	1:5	18.55	18.55	slightly hygroscopic; (monohydrate).
N-n-Hexyl 4-n-tridecylpyr. Br.	1:100M+	1:90M+	1:90M+	1:6M	97-98	1:20	18.7	18.7	slightly hygroscopic.
N-Alkyl Ethylpiperidinium: N- Cetyl-N-Methyl-2-ethylpiper. Br.	1:100M+	1:75M	1:50M	1:3M-	83-85	1:10	18.1	18.1	a hemihydrate.
N-Alkyl Amylpiperidinium: N- Lauryl-N-Methyl-4-n-amyl- piper. Br.	1:135M+	1:150M+	1:88M	1:9M	250	1:200	18.5	19.1	

*M=10³; +=actual value is higher, dilution not exactly determined; --=actual value is lower, dilution not exactly determined.

Although we have included in this table only halides in order to give basis for direct comparison, it should be understood that other salts are also active. The anion portion of the salt, whether organic or inorganic, should, of course, be one which gives a soluble salt and which is not of itself inconsistent with the use to be made of the salt or with other constituents with which it is to be used. Higher fatty acids generally are not desirable. Hydroxides are generally less stable and therefore less desirable than salts such as the halides.

In the accompanying drawings, Figs. 1, 2 and 3, we have charted available data for a series of compounds indicating definite test data by X's for *Staphylococcus aureus*, O's for *E. typhosa* at body temperature, □'s for *E. typhosa* at room temperature and Δ's for *E. typhosa* at room temperature in the presence of 10% serum, using arrows upwardly directed where values were determined only as above certain limits and downwardly directed arrows where they were determined only to be below the limits. We have also indicated for comparison the activities of some homologues of the various compounds next above and below the critical range. The heavy lines represent data on *Staphylococcus aureus* at body temperature, the light lines, data on *Eberthella typhosa* at body temperature, the dash line shows data on *E. typhosa* at 20° C. and the dot-dash line for *E. typhosa* at 20° C. in the presence of 10% serum.

From the charts the extraordinary increase in activity of the compounds of this type in the critical range is made strikingly evident.

Quaternary salts may be prepared readily from most 2, 3 or 4-alkyl or dialkyl pyridines by merely heating the appropriate pyridine compound with any primary alkyl halide at temperatures between 60° and 140° C. It is generally desirable to use as low a temperature as is convenient to avoid the side reactions which occur readily at higher tem-

peratures. Alkyl chlorides are of course much less reactive than the bromides or iodides and therefore require higher reaction temperatures and/or longer reaction times. The alkyl pyridine will usually react readily at these temperatures, unless the alkyl residue is attached to the 2-position of the pyridine ring in which case the reaction may be sluggish and require several days even at the higher reaction temperatures. In case this 2-alkyl group is a sterically large group such as the isopropyl or 3-pentyl group, the attachment of the alkyl halide to the pyridine nitrogen atom may be blocked altogether if alkyl chlorides are used, and seriously interfered with even when the more reactive bromides and iodides are used.

The products obtained are often very hygroscopic and low melting, as well as very soluble in most solvents such as water, alcohol, acetone, and ether. For this reason, they are usually difficult to isolate in pure crystalline form. Specific details for the preparation of several characteristic compounds are given below:

N-lauryl-4-n-butylpyridinium bromide.—A mixture of equimolar parts of lauryl bromide and 4-n-butylpyridine are heated for 48 hours at 100-110° C. The resulting thick oil is dissolved in about 2 volumes of ether, chilled to -20° C. and kept at this temperature overnight. The crystalline material is quickly filtered, and dried in vacuo at a low temperature. It may be recrystallized from ether in a similar manner. The pure product is very hygroscopic, melts at 58-60° C., and dissolves readily in water to give clear 20% solutions.

N-cetyl-2-ethylpyridinium bromide.—A mixture of equal molar parts of cetyl bromide and 2-ethylpyridine are heated for 15 to 20 hours at 110° C. The mixture is then recrystallized from ether in the usual manner to give a crystalline solid which melts at 88-90° C., and dissolves readily in water to give clear 20% aqueous solutions.

N-n-amy-2-n-undecylpyridinium bromide.—A mixture of equimolar parts of n-amy bromide and 2-n-undecyl pyridine are heated for 9 or 10 days at 80–85° C. The mixture is then dissolved in about two volumes of ether, chilled to –20° C. and allowed to crystallize. The product is filtered rapidly and dried in vacuo at a low temperature. The resulting solid is crystallized once more from ether to give a crystalline material, M. P. 55–58°, and very hygroscopic. It dissolves readily to give clear aqueous solutions.

N-n-decyl-4-n-hexylpyridinium bromide.—A mixture of equal molar parts of n-decyl chloride and 4-n-hexylpyridine was heated at 110° C. for 65–70 hours. The product was dissolved in alcohol and decolorized with charcoal. The alcohol was then evaporated and the residual oil washed several times with anhydrous ether. The product was dried in vacuo over sulfuric acid. The resulting oil resists attempts at crystallization, but contains the theoretical amount of bromine.

N-lauryl-4-n-amylypyridinium chloride.—A mixture of equal molar parts of lauryl chloride and 4-n-amylypyridine are heated for 20 hours at 135°. The resulting mixture is crystallized from ether at –20° C., filtered rapidly and dried in vacuo at 0° to 5° C. After a second recrystallization a pure crystalline product is obtained, M. P. 47–50°, which is extremely hygroscopic. It dissolves readily in water to give clear 20% solutions at 35°, or clear 2.5% solutions at 25°.

N-n-butyl-4-n-tridecylpyridinium bromide.—A mixture of 7½ parts of 4-n-tridecylpyridine and 3.9 parts of n-butyl bromide are heated at 75° for 36–48 hours. The resulting mixture may be dissolved in water, thoroughly mixed with Celite filter aid, a diatomaceous earth and then filtered. The resulting solution was satisfactory for disinfectant or germicidal purposes. If desired, reaction mixture may be dissolved in ether, chilled thoroughly and filtered while cold to give the crystalline butyl-tridecylpyridinium bromide which is a white solid, melting at about 65°, somewhat hygroscopic, and very soluble in water. Other tridecylpyridinium halides and other ring-substituted N-alkyl pyridiniums are prepared in an analogous manner.

The same principles which govern the preparation of the pyridinium salts apply also to preparation of piperidinium salts, although the piperidinium salts are often less soluble, higher melting and easier to isolate. The preparation of a few typical examples is described in detail below:

N-cetyl-N-methyl-2-ethylpiperidinium bromide.—A mixture of equimolar parts of cetyl bromide and N-methyl-2-ethylpiperidine are heated at 110° for 8 hours. The product is crystallized twice from acetone, washed with ether and dried to give a product melting at 83–85°. The material is readily soluble in water to give clear 10% solutions.

N-lauryl-N-methyl-4-n-amylypiperidinium bromide.—A mixture of equimolar parts of lauryl bromide and N-methyl-4-n-amylypiperidine are heated at 110° for 14 hours. The product was crystallized from acetone, washed with ether and dried to give a crystalline solid, M. P. 250° with decomposition. It is not readily soluble in water but forms clear solutions in 1:50000 concentration.

N-methyl-N-n-octyl-2-n-hexylpiperidinium bromide.—A mixture of equimolar parts of N-methyl-2-n-hexyl piperidine and n-octyl bromide are heated at 110° for 10 hours. The product is an

oil which resists attempts at crystallization. It is purified by washing with dry ether several times to give an oil soluble in 5 parts of water and containing 22.7% bromine. The calculated value is 22.4%.

The alkenyl and acylated compounds can be made in similar manner using the corresponding alkenyl or acylated halide compounds for reacting with the substituted pyridines; and the alkenyl and acyl pyridines may be used instead of the alkyl pyridines. Examples of the preparation of such compounds are:

N-cetyl-3-acetylpyridinium bromide.—A mixture of equimolar parts of cetyl bromide and 3-acetyl pyridine is heated at 75° C. for about 15 hours. The resulting crude product may be purified by recrystallization from ether in the usual manner. The purified material is a hygroscopic, crystalline solid. Melting at 65–69°. It forms a jelly with 10 parts of water, and dissolves readily to form mobile aqueous solutions of 1.0 to 0.5% concentration. Using myristyl bromide, the N-myristyl-3-acetyl-pyridinium bromide may be made, M. P. 101–103° C., water solubility 1:5.

N-n-propyl-2, 4-di-n-heptylpyridinium bromide.—A mixture of equimolar parts of n-propyl bromide and 2,4-di-n-heptylpyridine are refluxed or heated at 75–90° C. for several days until the reaction is at least 90% complete as evidenced by a determination of ionizable bromine in the reaction mixture. The product is then thoroughly washed with anhydrous ether to give an oily product, readily soluble in water to give clear solutions.

For ordinary germicidal and disinfecting purposes the compounds may be made up in water solutions of a strength, for example, 1:1,000 and diluted appropriately for the particular use to which it is to be put, or they may be furnished in more concentrated solution for appropriate dilution at the time of use. For treating hospital and sick room floors, walls, furniture and linen and patients' bed clothing, etc., an emulsion may be made with any desired strength, e. g., 1:500 of the quaternary ammonium compound, advantageously in accordance with the disclosure of the copending application of Manchey and Schneller, Serial No. 433,868, filed March 9, 1942, now Patent No. 2,372,159.

For sterilization of drinking water, the compounds of our invention are advantageously made up in tablets of appropriate size for the container in which the water is to be used. In view of the small amount of active compound required for such sterilization, and in order to improve tabletting and dissolution, it is ordinarily desirable to add a suitable diluent, for example, lactose. As one example, 45 parts of the N-alkyl alkyl pyridinium halide according to our invention is mixed with 50 parts of lactose and 5 parts of sugar syrup and this mixture is then formed into tablets of suitable size for dissolving in a canteen, jug, water barrel, or other container in which the water is to be sterilized, to give an effective sterilizing strength of the active ingredients, e. g., 1:10,000 with the better of our compounds.

These compounds may also be used in place of other quaternary ammonium compounds in various known pharmaceutical compositions and germicidal and disinfectant preparations. In particular these compounds may be used in any of the formulae set forth. They may be used in aqueous or oleaginous compositions as well as in organic solvents. They may be used in presence of acids or alkalis and with flavoring, coloring,

therapeutic or many other types of ingredients. They may be used as indicated above for sterilization, or disinfection and they may be used for preservation of foods, clothing, wood, adhesives, biological materials, and in general wherever decomposition or putrefaction might occur.

Illustrative of such compositions are:

Mouth wash

	Percent
Germicide	0.1-0.2
Boric acid	1
Alcohol	20-30
Flavor	as required
Color	as required
Water q. s.	100

Skin antiseptic

	Percent
Germicide	1-5
Dye	as required
Alcohol	40-50
Water q. s.	100

Cough drops

	Percent
Germicide	.1
Aromatics	as required
Sugar q. s.	100

Lipstick

	Percent
Germicide	.1
Beeswax	33
Lard	12
Castor oil	41
Lanolin	4
Water	4
Perfume and color q. s.	as required

Dentifrice

	Percent
Germicide	0.1
CaCO ₃	50
Tricalcium phosphate	25
Magnesium carbonate (or hydroxide)	24
Sugar saccharin and flavor	0.9
Wetting agent	0.1

Nose drops

	Percent
Germicide	0.03
Ephedrine SO ₄	1
Dextrose	4
Water q. s.	100

Germicidal ointment

	Percent
Germicide	0.2
Petrolatum	69
Lanolin	25
Water	6

Antiseptic medicated skin cream

	Percent
Germicide	0.1
Propylene glycol monostearate	10.0
Glycerin	5.0
Water	85.0

Lubricating jelly

	Percent
Germicide	0.1
Tragacanth	1.0
Glycerin	15.0
Water	100

These, of course, are only examples; and it should be understood that their proportions can

be varied substantially and that numerous other types of compositions are within the scope of the invention.

The compounds in the intermediate range referred to above are claimed in our co-pending continuation-in-part application, Serial No. 645,482 filed February 4, 1946, and claims directed to compounds of the present type wherein the "N" substituted group contains 3 carbon atoms and the substituent on the carbon atom of the ring has 13 carbon atoms are claimed in our co-pending continuation-in-part application, Serial No. 603,269 filed July 4, 1945.

We claim:

1. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring having five carbon atoms and the ammonium nitrogen, and aliphatic radicals of more than two carbon atoms each are attached to the ammonium nitrogen and to at least one of the carbon atoms of said ring respectively, the sum of the carbon atoms of said radicals being at least 17 and less than 20 when one of said aliphatic radicals contains 9 or 10 carbon atoms and being at least 16 and less than 19 when none of said aliphatic radicals contains 9 or 10 carbon atoms.

2. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring having five carbon atoms and the ammonium nitrogen, and having aliphatic radicals of more than two carbon atoms each attached to the ammonium nitrogen and to a carbon atom of said ring respectively, the sum of the carbon atoms of said radicals being 18 when one of said aliphatic radicals contains 9 or 10 carbon atoms and being 17 when none of said aliphatic radicals contains 9 or 10 carbon atoms.

3. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring having five carbon atoms and the ammonium nitrogen, and having alkyl radicals of more than two carbon atoms each attached to the ammonium nitrogen and to at least one of the carbon atoms of said ring respectively and the sum of the carbon atoms of said alkyl radicals being at least 17 and less than 20 when one of said alkyl radicals contains 9 or 10 carbon atoms and being at least 16 and less than 19 when none of said alkyl radicals contains 9 or 10 carbon atoms.

4. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring having five carbon atoms and the ammonium nitrogen, and alkyl radicals of more than two carbon atoms each attached to the ammonium nitrogen and to a carbon atom in the "2" position of said ring respectively and the sum of the carbon atoms of the attached radicals being at least 17 and less than 20 when one of said radicals contains 9 or 10 carbon atoms and being at least 16 and less than 19 when none of said alkyl radicals contains 9 or 10 carbon atoms.

5. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary am-

monium compound in which the heterocyclic nucleus is a six-membered ring having five carbon atoms and the ammonium nitrogen, and alkyl radicals of more than two carbon atoms each attached to the ammonium nitrogen and to a carbon atom in the "4" position of said ring respectively and the sum of the carbon atoms of the attached radicals being at least 17 and less than 20 when one of said radicals contains 9 or 10 carbon atoms and being at least 16 and less than 19 when none of said alkyl radicals contains 9 or 10 carbon atoms.

6. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group including said nitrogen atom and an aliphatic radical, and a lower aliphatic radical of at least two carbon atoms is attached to a carbon atom of the nucleus, the sum of the carbon atoms of all the radicals of at least two carbon atoms attached to said ring being at least 16 and less than 19.

7. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group including said nitrogen atom and a higher aliphatic radical of more than ten carbon atoms, and a lower alkyl radical of at least two carbon atoms is attached to a carbon atom of the nucleus, the sum of the carbon atoms of the radicals attached to the ring being at least 16 and less than 19.

8. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group including said nitrogen atom and a higher aliphatic radical of more than ten carbon atoms, and a lower alkyl radical of at least two carbon atoms is attached to the carbon atom in a "2" position of the nucleus, the sum of the carbon atoms of the radicals attached to the ring being at least 16 and less than 19.

9. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group including said nitrogen atom and a higher aliphatic radical of more than ten carbon atoms, and a lower alkyl radical of at least two carbon atoms is attached to the carbon atom in the "4" position of the nucleus, the sum of the carbon atoms of the radicals attached to said ring being at least 16 and less than 19.

10. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a pyridinium compound in which a higher aliphatic radical of more than ten carbon atoms is attached to the nitrogen atom of the pyridinium nucleus and an alkyl radical of at least two and less than eight carbon atoms is attached to a carbon atom of the nucleus, the sum of the carbon atoms in said radicals being at least 16 and less than 19.

11. A germ-counteracting composition which

comprises, as the essential germ-counteracting ingredient thereof, a piperidinium compound in which a higher aliphatic radical of more than ten carbon atoms is attached to the nitrogen atom of the piperidinium nucleus and an alkyl radical of at least two and less than eight carbon atoms is attached to a carbon atom of the nucleus, the sum of the carbon atoms in said radicals being at least 16 and less than 19.

12. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a N-higher alkyl 4-lower alkyl piperidinium compound, the sum of the carbon atoms in said higher and lower alkyl groups being at least 16 and less than 19.

13. A germ-counteracting composition which comprises as the essential germ-counteracting ingredient thereof, a N-lauryl 4-n-amyl pyridinium compound.

14. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a N-lauryl N-methyl 4-n-amyl piperidinium compound.

15. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group includes besides said nitrogen atom an aliphatic radical of at least two and less than nine carbon atoms and an aliphatic radical of at least eleven carbon atoms is attached to a carbon atom of the nucleus, the sum of the carbon atoms of said radicals being at least 16 and less than 20.

16. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group includes besides said nitrogen atom an alkyl radical of at least two and less than nine carbon atoms, and an aliphatic radical of at least eleven carbon atoms is attached to a carbon atom of the nucleus, the sum of the carbon atoms of said radicals being at least 16 and less than 20.

17. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group includes besides said nitrogen atom an alkyl radical of at least two and less than nine carbon atoms, and an aliphatic radical of at least eleven carbon atoms is attached to the carbon atom in a "2" position of the nucleus, the sum of the carbon atoms of said radicals being at least 16 and less than 20.

18. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a heterocyclic quaternary ammonium compound in which the heterocyclic nucleus is a six-membered ring of five carbon atoms and the ammonium nitrogen atom, the ammonium group includes besides said nitrogen atom an alkyl radical of at least two and less than nine carbon atoms, and an aliphatic radical of at least eleven carbon atoms is attached to the carbon atom in the "4" position of the nucleus, the sum of the carbon atoms of said radicals being at least 16 and less than 20.

19. A germ-counteracting composition which comprises, as the essential germ-counteracting

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ingredient thereof, a pyridinium compound in which an alkyl radical of more than two and less than nine carbon atoms is attached to the nitrogen atom of the pyridinium nucleus, and a higher aliphatic radical is attached to one of the carbon atoms of the pyridinium nucleus, the sum of the carbon atoms in said radicals being at least 16 and less than 19.

20. A germ-counteracting composition which comprises, as the essential germ-counteracting ingredient thereof, a N-alkyl tridecyl pyridinium compound, the N-alkyl group having not less than three nor more than six carbon atoms.

21. A germ-counteracting composition which

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comprises, as the essential germ-counteracting ingredient thereof, a N-butyl 4-n-tridecyl pyridinium compound.

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REFERENCES CITED

The following references are of record in the file of this patent:

FOREIGN PATENTS

Number	Country	Date
479,925	Great Britain	May 11, 1936