*Anal.* Calcd. for $C_{10}H_{13}ON$: N, 8.58. Found: N, 8.55.

**3-*n*-Amylpyridine.**—To 55 g. (0.337 mole) of 3-valerylpyridine was added 0.675 mole of semicarbazide hydrochloride and 0.7 mole of sodium acetate. The mixture was refluxed for one hour, then diluted with a large volume of water and chilled. The resulting solid semicarbazone was filtered and dried *in vacuo* over concentrated sulfuric acid to yield 53 g., m.p. 177–179°.

The semicarbazone was added to a mixture of 45 g. of 85% aqueous hydrazine hydrate and 80 g. of sodium methoxide in 1250 ml. of methanol. The mixture was heated at 200° for 8 hr. in an autoclave, acidified with aqueous hydrochloric acid, and then heated on a steam-bath to remove the methanol. The last traces of methanol were removed by gentle warming over a flame. The residue was cooled and a cold solution of sodium hydroxide was added until the mixture was alkaline. The 3-*n*-amylpyridine was extracted with ether, dried over potassium hydroxide pellets and distilled to give 29 g. (81%) of product boiling at 224–226° (748 mm.); $n^{25}D$ 1.4892.

*Anal.* Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.29.

## Discussion

The data in Table I show that the most important factor determining germicidal activity is the total number of carbon atoms in $R^1$ and $R^2$, the C-alkyl and N-alkyl groups, and not the length of the higher molecular weight chain alone. Maximum activity was obtained in all series when the carbon total was 16 to 19. Above and below this critical carbon total, activity decreased sharply. In general, 4-substituted pyridinium salts are more active, at peak activity, than the corresponding 2-substituted compounds. The 4-substituted isomers are also much less soluble than the 2-substituted compounds.

In the single series of 2-, 3- and 4-amylpyridine salts, the most active 3-substituted compound, No. 30, showed approximately the same germicidal activity as the most active 4-substituted compound, No. 37. The 3-acylpyridinium salts appear to be less active than comparable 3-alkylpyridine compounds.

Branching of the carbon substituent influenced germical activity according to the degree of branching. Slightly branched chains, such as the 4-(2-methyloctyl) group, showed a peak activity comparable with that of the unbranched 4-*n*-nonyl group, while the more highly branched 4-(5-nonyl) group gave a definitely lower peak. An unsaturated sidechain, No. 21, gave a peak activity approximately equal to the corresponding saturated compound, No. 22.

The nature of the anion did not greatly influence germicidal activity, as is demonstrated by a comparison of compounds No. 7 and No. 8 or No. 35 and No. 36. Similar compounds containing sulfate, nitrate and benzoate anions, also prepared in this Laboratory, were found to be of the same order of activity.

In the range of peak activity for each series of salts, the germicidal activity against Gram-negative organisms (*E. typhosa*) approaches or equals potency against Gram-positive organisms (*Staph. aureus*), although with quaternary ammonium salts in general the Gram-negative activity is somewhat lower. Other advantages of the ring-substituted pyridinium compounds are the retention of high germicidal activity at room temperature, a surprising immunity to the presence of serum,[4] and a general lack of increase of intraperitoneal toxicity in rats with an increase in germicidal potency.

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[CONTRIBUTION FROM THE ORGANIC DEPARTMENT, RESEARCH LABORATORIES, THE WM. S. MERRELL COMPANY]

# Quaternary Ammonium Salts as Germicides. V. Quaternary Ammonium Salts Derived from Substituted Piperidines

BY G. H. HARRIS,[1] R. S. SHELTON, M. G. VAN CAMPEN AND E. L. SCHUMANN

Investigations of the germicidal properties of quaternary ammonium compounds have been extended to include C-alkyl piperidinium salts. Results of germicidal tests with these compounds show that peak activity occurs when the sum of the carbon atoms in the C-alkyl and N-alkyl groups is in the region of seventeen to nineteen and indicate a definite relationship between molecular size and germicidal activity analogous to that found with C-alkyl pyridinium salts.

The preceding paper[2] in this series described the relation of structure to germicidal activity of a series of substituted pyridinium salts. As an extension of this work, the present report is concerned with quaternary ammonium salts of C-substituted piperidines and their germicidal activity. A series of piperidinium salts has been prepared in which the C-alkyl group size has been varied in length from two to thirteen carbon atoms. The position of the carbon substituent, the size of the N-alkyl groups and, in one case, the anion have also been varied.

Physical properties and germicidal activity data for the piperidinium salts are compiled in Table II. Reaction conditions and recrystallization solvents are given in Table III and new piperidine intermediates are listed in Table I. Several piperidinium salts were isolated as hydrates, as shown in Table II. The degree of hydration was proved as described in the preceding paper.[2]

## Experimental

Alkylpiperidine intermediates were prepared by two methods. In the first, alkylpyridines were catalytically hydrogenated and the resulting alkylpiperidines were then N-alkylated by means of formaldehyde and formic acid or a suitable alkyl halide. In the second method, alkylpyridine

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TABLE I

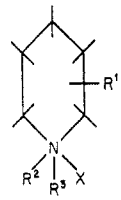
PROPERTIES OF INTERMEDIATE PIPERIDINES

| Compound, piperidine | Formula | B.p.,[a] °C. | Mm. | Neut. equiv. Calcd. | Neut. equiv. Obsd. | $n^{25}D$ | Yield, % |
|---|---|---|---|---|---|---|---|
| 4-Ethyl- | $C_7H_{15}N$ | 154–155 | 743 | 113 | 113 | 1.4503 | 50 |
| 1-Methyl-4-ethyl- | $C_8H_{17}N$ | 151–152 | 750 | 127 | 129 | 1.4400 | 89 |
| 1-Methyl-2-*n*-amyl- | $C_{11}H_{23}N$ | 96–97 | 19 | 169 | 166 | | |
| 1-Methyl-4-*n*-amyl- | $C_{11}H_{23}N$ | 120 | 35 | 169 | 171 | 1.4501 | 64 |
| 1-Ethyl-4-*n*-amyl- | $C_{12}H_{25}N$ | 107–110 | 13–15 | 183 | 182 | 1.4530 | |
| 1-*n*-Butyl-4-*n*-amyl- | $C_{14}H_{29}N$ | 160 | 38 | 211 | 210 | 1.4528 | 100 |
| 1-*n*-Decyl-4-*n*-amyl- | $C_{20}H_{41}N$ | 175 | 4 | 295 | 297 | 1.4587 | 97 |
| 1-Lauryl-4-*n*-amyl- | $C_{22}H_{45}N$ | 197–199 | 2.5 | | [c] | 1.4607 | 96 |
| 1-Methyl-2-*n*-hexyl- | $C_{12}H_{25}N$ | 107 | 11 | 183 | 185 | 1.4548 | 78 |
| 4-*n*-Undecyl- | $C_{16}H_{33}N$ | 148 | 3.5[b] | 239 | 235 | | 86 |
| 1-Methyl-4-*n*-undecyl- | $C_{17}H_{35}N$ | 143 | 2.5 | 253 | 256 | 1.4596 | 91 |
| 1-Methyl-4-*n*-tridecyl- | $C_{19}H_{39}N$ | 143–145 | 1 | 282 | 282 | 1.4592 | 53 |

[a] All temperatures are uncorrected. [b] Solidified; m.p. 25–30°. [c] The base was too weak for a neutral equivalent determination. Accordingly, the hydrochloride was prepared and the equivalent weight of the salt was determined. Equiv. wt. Calcd. for $C_{22}H_{45}N\cdot HCl$: equiv. wt., 360. Found: equiv. wt., 359.

TABLE II

PROPERTIES OF SUBSTITUTED PIPERIDINE QUATERNARY SALTS




| No. | $R^1$ | $R^2$ | $R^3$ | X | M.p., °C. | Formula | Halogen, % Calcd. | Halogen, % Obsd. | Soly.[a] in $H_2O$ | Total C in $R^1$, $R^2$, $R^3$ | Germicidal activity × $10^{3b}$ *Staph. aureus* 37° | Germicidal activity × $10^{3b}$ *E. typhosa* 37° |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ethylpiperidine salts | | | | | | | |
| 1 | 2-Ethyl | Methyl | Cetyl | Br | 83–85 | $C_{24}H_{50}NBr$ | 18.1[c] | 18.1 | 10 | 19 | 120 | 50 |
| 2 | 4-Ethyl | Methyl | Myristyl | Br | 214–216 | $C_{22}H_{46}NBr$ | 19.75 | 19.60 | 5 | 17 | 190 | 170 |
| 3 | 4-Ethyl | Methyl | Cetyl | Br | 215–217 | $C_{24}H_{50}NBr$ | 18.5 | 18.4 | 10 | 19 | 125 | 60 |
| | | | | | Amylpiperidine salts | | | | | | | |
| 4 | 2-*n*-Amyl | Methyl | Lauryl | Br | 75–78 | $C_{23}H_{48}NBr$ | 18.7[c] | 18.7 | 5 | 18 | 170 | 90 |
| 5 | 4-*n*-Amyl | Methyl | *n*-Octyl | Br | 255–256[d] | $C_{19}H_{40}NBr$ | 21.0[e] | 21.3 | 100 | 14 | <50 | <30 |
| 6 | 4-*n*-Amyl | Methyl | *n*-Decyl | Br | 248–250 | $C_{21}H_{44}NBr$ | 20.5 | 20.5 | 300 | 16 | <50 | 47 |
| 7 | 4-*n*-Amyl | Methyl | Lauryl | Br | 250 dec. | $C_{23}H_{48}NBr$ | 18.3[c] | 18.5 | 200 | 18 | 135 | 150 |
| 8 | 4-*n*-Amyl | Methyl | Myristyl | Br | 244–246 | $C_{25}H_{52}NBr$ | 17.6[c] | 17.6 | 3000 | 20 | >100 | >90 |
| 9 | 4-*n*-Amyl | Ethyl | Lauryl | Br | 246–247[d] | $C_{24}H_{50}NBr$ | 18.5 | 18.5 | 1500 | 19 | 150 | 140 |
| 10 | 4-*n*-Amyl | *n*-Butyl | *n*-Decyl | Br | 181–183 | $C_{24}H_{50}NBr$ | 18.5 | 18.5 | 600 | 19 | 90 | <50 |
| 11 | 4-*n*-Amyl | *n*-Butyl | Lauryl | Br | 175–177 | $C_{26}H_{54}NBr$ | 16.75[e] | 16.9 | 1400 | 21 | 150 | 75 |
| | | | | | Hexylpiperidine salts | | | | | | | |
| 12 | 2-*n*-Hexyl | Methyl | *n*-Octyl | Br | Oil | $C_{20}H_{42}NBr$ | 21.3 | 21.5 | 5 | 15 | <50 | <30 |
| 13 | 2-*n*-Hexyl | Methyl | Lauryl | Br | 94–96 | $C_{24}H_{50}NBr$ | 18.5 | 18.5 | 5 | 19 | <55 | 30 |
| 14 | 2-*n*-Hexyl | Methyl | Myristyl | Br | 92–93 | $C_{26}H_{54}NBr$ | 17.4 | 17.3 | 5 | 21 | 67 | 50 |
| 15 | 2-*n*-Hexyl | Methyl | Cetyl | Br | 73–75 | $C_{28}H_{58}NBr$ | 15.8[c] | 15.8 | 5 | 23 | <50 | <30 |
| | | | | | Undecylpiperidine salts | | | | | | | |
| 16 | 4-*n*-Undecyl | Methyl | *n*-Amyl | Br | 225–228 | $C_{22}H_{46}NBr$ | 19.8 | 19.8 | 10 | 17 | 170 | 160 |
| 17 | 4-*n*-Undecyl | Methyl | *n*-Hexyl | Br | 230–232 | $C_{23}H_{48}NBr$ | 19.1 | 19.1 | 350 | 18 | 170 | 180 |
| 18 | 4-*n*-Undecyl | Methyl | *n*-Heptyl | Br | 232–234 | $C_{24}H_{50}NBr$ | 18.5 | 18.6 | 550 | 19 | >150 | 160 |
| 19 | 4-*n*-Undecyl | Methyl | *n*-Octyl | Br | 234–237 | $C_{25}H_{52}NBr$ | 17.55[c] | 17.55 | <1000 | 20 | 180 | 120 |
| | | | | | Tridecylpiperidine salts | | | | | | | |
| 20 | 4-*n*-Tridecyl | Methyl | Allyl | Cl | 170–172 | $C_{22}H_{44}NCl$ | 9.91 | 9.91 | 5 | 17 | 67 | 75 |
| 21 | 4-*n*-Tridecyl | Methyl | *n*-Propyl | Br | 200–202 | $C_{22}H_{46}NBr$ | 19.8 | 19.7 | 5 | 17 | 120 | 55 |
| 22 | 4-*n*-Tridecyl | Methyl | *n*-Butyl | Br | 210–212 | $C_{23}H_{48}NBr$ | 19.1 | 19.1 | 5 | 18 | | |

[a] Approximate parts of water required to dissolve one part of the salt at room temperature; solubilities were not determined for concentrations greater than 1:5. [b] The values given × $10^3$ represent Critical Killing Dilutions. A value of 100, for example, means that the C. K. D. is 1:100 × $10^3$. C. K. D. is that dilution of the substance which will kill organisms of standard phenolic resistance in 10 minutes, but not in 5, by the technique described for the determination of phenol coefficients in Circular 198 of the U. S. Department of Agriculture. [c] Hemihydrate. [d] Melts with decomposition; a preheated bath was used. [e] Monohydrate.

TABLE III

EXPERIMENTAL CONDITIONS

| No.[a] | Bromide used | Time,[b] hr. | Temp.,[c] °C. | Reacted,[d] % | Recrystn. solvent |
|---|---|---|---|---|---|
| 1 | Cetyl | 13 | 110 | 95 | Acetone |
| 2 | Myristyl | 216 | 75 | | Acetone |
| 3 | Cetyl | 216 | 75 | | Acetone |
| 4 | Lauryl | 214 | 75 | | Acetone–$Et_2O$ |
| 5 | *n*-Octyl | 10 | 110 | 93 | Butanone |
| 6 | *n*-Decyl | 240 | 75 | | Butanone |
| 7 | Lauryl | 14 | 110 | 90 | Acetone |
| 8 | Myristyl | | 75 | | Butanone |
| 9 | Ethyl | [e] | [e] | | Acetone |
| 10 | *n*-Decyl | [f] | 110 | | Acetone–$Et_2O$ |
| 11 | *n*-Butyl | [f] | 110 | 84 | Acetone–$Et_2O$ |
| 12 | *n*-Octyl | 8 | 110 | 100 | Abs. $Et_2O$ wash |
| 13 | Lauryl | 8 | 110 | 100 | Acetone |
| 14 | Myristyl | 8 | 110 | 100 | Acetone |
| 15 | Cetyl | 8 | 110 | 100 | Acetone |
| 16 | *n*-Amyl | 120 | 70 | | Acetone |
| 17 | *n*-Hexyl | | 75 | | Acetone |
| 18 | *n*-Heptyl | 120 | 70 | | Acetone |
| 19 | *n*-Octyl | 144 | 70 | | Acetone |
| 20 | Allyl chloride | 30 | 70 | | Acetone |
| 21 | *n*-Propyl | 168 | 70 | | Acetone |
| 22 | *n*-Butyl | 168 | 70 | | Acetone |

[a] The numbers refer to compounds listed in Table II. [b] Reaction time. [c] Reaction temperature. [d] Based on a determination of ionizable halogen in a weighed sample of the reaction mixture. [e] 48 hr. at 80°, then 4 hr. at 110°. [f] Several days.

quaternary ammonium salts were hydrogenated to give the N-substituted alkylpiperidine directly. Physical constants of new piperidine intermediates are listed in Table I. Piperidines not listed in Table I have been described previously or were obtained from the Reilly Tar and Chemical Corporation.

**Hydrogenation of Alkylpyridines.**—The alkylpyridine was dissolved in absolute ethanol to which a chemically equivalent amount of concentrated hydrochloric acid was added. The mixture was hydrogenated in the presence of platinum catalyst at room temperature under a pressure of one to three atmospheres. After cessation of hydrogen absorption, the mixture was filtered and evaporated. The residue was treated with excess aqueous alkali, the amine was extracted with ether, and the ether solution was dried over anhydrous sodium sulfate or sodium hydroxide. After filtration and removal of the ether, the alkylpiperidine was distilled.

Compounds prepared in this way were 4-ethylpiperidine and 4-*n*-undecylpiperidine.

**N-Alkylation of Alkylpiperidines.**—Ring-substituted piperidines were N-methylated by refluxing a mixture of 0.2 mole of the piperidine, 45 cc. of 90% formic acid, 28 cc. of 37% formaldehyde solution and 120 cc. of water for 18 hours. After cooling, the mixture was made strongly alkaline with 50% aqueous sodium hydroxide and the amine was extracted with ether. The ether extract was dried over potassium hydroxide, filtered and fractionally distilled.

Intermediates prepared using this method were 1-methyl-4-ethylpiperidine, 1-methyl-2-*n*-amylpiperidine, 1-methyl-4-*n*-amylpiperidine, 1-methyl-2-*n*-hexylpiperidine and 1-methyl-4-*n*-undecylpiperidine.

**1-Ethyl-4-*n*-amylpiperidine.**—Equimolar amounts of 4-*n*-amylpiperidine and ethyl bromide in an equal volume of ether were refluxed for one-half hour. An equivalent amount of sodium hydroxide in water solution was then added and refluxing was continued overnight. The ether layer was then separated and distilled.

**Direct Hydrogenation of Pyridinium Salts.**—Alkylpyridines were first allowed to react with a suitable alkyl halide by methods described in the previous paper in this series.[2] The resulting pyridinium salt was dissolved in absolute ethanol and a very small amount of concentrated hydrochloric acid was added. The mixture was then hydrogenated in the presence of platinum catalyst at one to three atmospheres pressure. After hydrogen absorption ceased, the catalyst was removed by filtration and the filtrate was made alkaline. The amine was extracted with ether, dried over potassium hydroxide and fractionally distilled.

Piperidines prepared by direct hydrogenation, in this manner, were 1-*n*-butyl-4-*n*-amylpiperidine, 1-*n*-decyl-4-*n*-amylpiperidine, 1-lauryl-4-*n*-amylpiperidine and 1-methyl-4-*n*-tridecylpiperidine.

**Preparation of Piperidinium Salts.**—Quaternary ammonium salts were prepared by heating equimolar amounts of the alkylpiperidine and a suitable alkyl halide in a closed vessel. After the reaction was complete, as determined by a titration for halogen of a sample of the reaction mixture, the product was recrystallized. Reaction time, reaction temperature and recrystallization solvent for each compound are given in Table III. The products were usually white, crystalline solids, occasionally hygroscopic. A few were isolated in hydrated forms, as indicated in Table II.

## Discussion

The remarks made in the previous paper concerning structure–activity relationships of the substituted pyridinium salts are applicable, in general, to the piperidinium salts described here. In Table II, the compounds are arranged in groups according to size and position of the ring substituent. Within the groups, the salts are listed in order of increasing size of the N-alkyl radicals. In each group the data show that germicidal activity increases to a peak, then decreases. Peak activity is reached, in most cases, when the sum of the carbon atoms in $R^1$, $R^2$ and $R^3$ is in the region of seventeen to nineteen. The correlation of carbon atom total and germicidal activity is not as close as in the previously described pyridine series since the piperidinium compounds contain an additional alkyl group which complicates the relationship.

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