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Quaternary Ammonium Salts as Germicides. IV. Quaternary Ammonium Salts Derived from Substituted Pyridines

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A series of C-alkyl pyridinium salts has been prepared and tested in a search for more effective germicides. Maximum activity occurs when the sum of the carbon atoms in the C-alkyl and N-alkyl groups is from sixteen to nineteen. Within this range, activity is less dependent upon chain branching, position isomerism or the nature of the anion.

Earlier investigations in this Laboratory[2a,2b,3] have been concerned with the relation of the molecular structure of quaternary ammonium salts to their germicidal activity. Since it was found that quaternary salts of pyridine and various methylpyridines were active germicides, the study was extended to include alkylpyridines in which the alkyl groups contain two to seventeen carbon atoms and also to include acylpyridines. A rather extensive series of compounds was prepared in which the size and position of the carbon substituent, the N-alkyl group and the anion were varied. These structure changes, together with germicidal activity data, give a ready means of correlating structure with activity. Patents[4] have been granted covering the compounds described here.

The germicidal activity of a number of quaternary ammonium salts of nicotinamide and N-substituted nicotinamides[5] was described in a recent publication, but no unusual potency was obtained. Another publication[6] described quaternary salts of nicotinamide and nicotinic acid but no germicidal data were given. Lo Cicero, Frear and Miller[7] reported the fungicidal activity of a number of alkylpyridinium salts, some of which were covered by the patents cited above. No germicidal activities were included in the study.

The pyridinium salts were prepared by the well known method of heating a substituted pyridine with an alkyl halide for varying lengths of time at various temperatures. In general, the pyridinium salts were relatively low melting, white, crystalline solids. Most of the salts were hygroscopic, some exceedingly so, and were soluble in five to ten parts of water at room temperature. Most of the compounds were recrystallizable from ether or acetone and ether.

Several of the compounds were isolated as hydrates which is in agreement with the known tendency of 1-alkylpyridinium salts to crystallize as hydrates.[8] The hydration of a few representative compounds was determined by drying samples *in vacuo* over phosphorus pentoxide for two to three weeks. The loss of weight and the change in halogen content indicated the degree of hydration as shown in Table I.

Properties of the quaternary salts, including germicidal activity, are summarized in Table I. Since reaction time, reaction temperature and purification procedures varied considerably for the individual compounds, the pertinent information has been compiled in Table II.

Experimental

The alkylpyridines used in this work were obtained from the Reilly Tar and Chemical Corporation. Additional supplies of several of the pyridines were prepared by means of the Chichibabin reaction.[9] The preparations of 3-valerylpyridine and 3-*n*-amylpyridine, new intermediates, are given below.

Quaternary salts of the various substituted pyridines were generally prepared by heating equimolar quantities of an appropriate pyridine with a primary alkyl halide in a closed vessel at temperatures between 60 and 135°. In a few cases the reaction was carried out at room temperature and occasionally a solvent such as methanol or ethanol was used. Alkyl chlorides required higher reaction temperatures than bromides. More drastic conditions were also needed when α-alkylpyridines were used. The products obtained were often very hygroscopic, low melting and soluble in most solvents such as water, alcohol, acetone and ether. Three purification methods are given below.

Method A.—The reaction mixture was merely washed with a cold solvent or recrystallized as indicated in Table II. Usually only two or three volumes of solvent were necessary and extreme cooling was used to precipitate the product. The salts obtained were dried *in vacuo* over phosphorus pentoxide or concentrated sulfuric acid. Occasionally it was necessary to conduct this drying procedure at refrigerator temperatures to preserve the crystalline nature of the product.

Method B.—When the reaction mixture assumed a dark color during heating, the crude product was dissolved in methanol and decolorized with charcoal. The methanol was removed by heating the mixture on a steam-bath under an air jet and the crude salt was then recrystallized or washed and dried *in vacuo*.

Method C.—If hydrohalides of the substituted pyridines were obtained as by-products, they were removed by the following method. The reaction product was dissolved in methanol and a few drops of phenolphthalein were added. The solution was then titrated with sodium hydroxide solution until a dark color was obtained. The color change was sharp and was not due entirely to the indicator. After decolorization with charcoal, the methanol was removed as described in Method B and the product was recrystallized. It was necessary to remove sodium halide impurities by dissolving the product in acetone, filtering and removing the acetone before recrystallizing. Yields of pure pyridinium salts varied from 5 to 50%, depending upon side reactions and recrystallization losses.

3-Valerylpyridine.—To 64 g. (1.13 moles) of 95% sodium methoxide was added fairly rapidly a solution of 103 g. (0.75 mole) of methyl nicotinate in 106 g. (1.43 moles) of methyl acetate. The mixture was stirred one-half hour, then refluxed for ten hours. Volatile material was removed under reduced pressure, leaving the crude methyl 3-pyridyl-3-ketopropionate sodium enolate. Absolute ethanol and a large excess of *n*-propyl bromide were added, and the mixture was allowed to stand for several days until a neutral solution was obtained. After dilution with water, the mixture was acidified with 250 ml. of concentrated hydrochloric acid and refluxed for three hours. The solution was then rendered alkaline and extracted with ether. Two fractional

(1) Great Western Division, The Dow Chemical Company, Pittsburg, California.

(2a) Shelton, *et al.*, THIS JOURNAL, **68**, 753 (1946).

(2b) Shelton, *et al.*, *ibid.*, **68**, 755 (1946).

(3) Shelton, *et al.*, *ibid.*, **68**, 757 (1946).

(4) U. S. Patents 2,446,792, 2,446,793 and 2,446,796.

(5) Zienty, *J. Am. Pharm. Assoc., Sci. Ed.*, **37**, 99 (1948).

(6) Gautier and Renault, *Compt. rend.*, **226**, 1736 (1948).

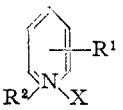
(7) Lo Cicero, Frear and Miller, *J. Biol. Chem.*, **172**, 689 (1948).

(8) Kolloff, Wyss, Himelick and Mantele, *J. Am. Pharm. Assoc.*, **31**, 51 (1942).

(9) Chichibabin, *Bull. soc. chim.*, [5] **3**, 777 (1936).

TABLE I

PROPERTIES OF SUBSTITUTED PYRIDINE QUATERNARY SALTS



No.	R^1	R^2	X	M.p. °C.[a]	Formula	Halogen, % Calcd.	Halogen, % Obsd.	Soly. in H_2O[b]	Total carbons in R^1 and R^2	Germicidal activity × 10^{3c} *Staph. aureus* 37°	Germicidal activity × 10^{3c} *E. typhosa* 37°
					Ethylpyridine salts						
1	2-Ethyl	Myristyl	Br	70–72	$C_{21}H_{38}NBr$	20.30[d]	20.35	5	16	>100	>90
2	2-Ethyl	Cetyl	Br	88–90	$C_{23}H_{42}NBr$	19.4	19.5	5	18	>100	>75
3	2-Ethyl	Stearyl	Br	95–96	$C_{25}H_{46}NBr$	17.4[e]	17.4	10	20		
4	4-Ethyl	*n*-Octyl	Br	41–44	$C_{15}H_{26}NBr$	26.6	26.6	5	10	<50	<30
5	4-Ethyl	Lauryl	Br	43–44	$C_{19}H_{34}NBr$	22.4	22.3	5	14	<50	50
6	4-Ethyl	Myristyl	Br	50–52	$C_{21}H_{38}NBr$	20.3[d]	20.3	5	16	92	>130
7	4-Ethyl	Cetyl	Cl	67–70	$C_{23}H_{42}NCl$	9.63	9.54	5	18	>100	78.5
8	4-Ethyl	Cetyl	Br	67–69	$C_{23}H_{42}NBr$	19.4	19.3	25	18	>90	82
9	4-Ethyl	Stearyl	Br	79–81	$C_{25}H_{46}NBr$	18.14	18.05	[f]	20		
					Propylpyridine salts						
10	2-Isopropyl	Lauryl	Br	55–56	$C_{29}H_{36}NBr$	21.6	21.6	5	15	<50	<30
11	2-Isopropyl	Cetyl	I	58–62	$C_{24}H_{44}NI$	26.8	26.8	>2000	19	<50	<40
12	4-*n*-Propyl	*n*-Octyl	Br	36–38	$C_{18}H_{28}NBr$	25.4	25.4	5	11	<50	<30
13	4-*n*-Propyl	*n*-Decyl	Br	[g]	$C_{18}H_{32}NBr$	23.35	23.55	5	13	<50	<30
14	4-*n*-Propyl	Lauryl	Br	40–42	$C_{20}H_{36}NBr$	21.6	21.6	5	15	<50	64
15	4-*n*-Propyl	Myristyl	Br	64–67	$C_{22}H_{40}NBr$	20.1	19.9	5	17	>140	>130
16	4-*n*-Propyl	Cetyl	Br	63–66	$C_{24}H_{44}NBr$	18.7	18.7	100	19	50	67
					Butylpyridine salts						
17	4-*n*-Butyl	*n*-Octyl	Br	Oil	$C_{17}H_{30}NBr$	24.3	24.2	5	12	<50	30
18	4-*n*-Butyl	*n*-Decyl	Br	Oil	$C_{19}H_{34}NBr$	22.4	22.7	5	14	90	100
19	4-*n*-Butyl	Lauryl	Cl	30	$C_{21}H_{38}NCl$	10.43	10.36	5	16		
20	4-*n*-Butyl	Lauryl	Br	58–60	$C_{21}H_{38}NBr$	20.8	20.7	5	16	>100	90
21	4-*n*-Butenyl	Myristyl	Br	57–59	$C_{23}H_{40}NBr$	19.45	19.35	5	18	140	150
22	4-*n*-Butyl	Myristyl	Br	75–77	$C_{23}H_{42}NBr$	19.0[d]	19.0	5	18	130	>90
23	4-*n*-Butyl	Cetyl	Br	54–56	$C_{25}H_{46}NBr$	18.1	18.1	300	20	<50	50
					Amylpyridine salts						
24	2-*n*-Amyl	*n*-Octyl	Br	Oil	$C_{18}H_{32}NBr$	23.3	24.3	5	13	<50	<30
25	2-*n*-Amyl	*n*-Decyl	Br	Oil	$C_{20}H_{36}NBr$	21.6	22.6	5	15	<50	<30
26	2-*n*-Amyl	Lauryl	Br	67–69	$C_{22}H_{40}NBr$	20.05	20.40	5	17	75	>100
27	2-*n*-Amyl	Myristyl	Br	69–71	$C_{24}H_{44}NBr$	18.75	18.85	10	19	130	70
28	2-*n*-Amyl	Cetyl	Br	71–74	$C_{26}H_{48}NBr$	17.58	17.53	5	21	70	<30
29	3-*n*-Amyl	*n*-Decyl	Br	30	$C_{20}H_{36}NBr$	21.6	21.7	5	15	<50	50
30	3-*n*-Amyl	Lauryl	Br	50–51	$C_{22}H_{40}NBr$	20.05	20.05	5	17	170	>200
31	3-*n*-Amyl	Myristyl	Br	38–40	$C_{24}H_{44}NBr$	18.75	18.75	5	19	140	50
32	4-Isoamyl	Myristyl	Cl	30	$C_{24}H_{44}NCl$	9.28	9.26	5	19	120	130
33	4-*n*-Amyl	*n*-Octyl	Br	Oil	$C_{18}H_{32}NBr$	23.3	23.4	40	13	<50	<30
34	4-*n*-Amyl	*n*-Decyl	Br	Oil	$C_{20}H_{36}NBr$	21.6	21.7	50	15	<50	<50
35	4-*n*-Amyl	Lauryl	Cl	49–51	$C_{22}H_{40}NCl$	10.01	9.97	30	17	>130	>130
36	4-*n*-Amyl	Lauryl	Br	85–87	$C_{22}H_{40}NBr$	20.05	20.00	35	17	140	130
37	4-*n*-Amyl	Myristyl	Br	85–90	$C_{24}H_{44}NBr$	18.75	19.3	>500	19	170	130
38	4-*n*-Amyl	Cetyl	Br	107–109	$C_{26}H_{48}NBr$	17.58	17.55	575	21	90	<30
					Hexylpyridine salts						
39	2-*n*-Hexyl	*n*-Octyl	Br	Oil	$C_{19}H_{34}NBr$	22.4	22.5	5	14	<50	<30
40	2-*n*-Hexyl	*n*-Decyl	Br	Oil	$C_{21}H_{38}NBr$	20.8	21.9	5	16	<50	60
41	2-*n*-Hexyl	Lauryl	Br	76–78	$C_{23}H_{42}NBr$	19.38	19.33	5	18	108	94
42	2-*n*-Hexyl	Myristyl	Br	[h]	$C_{25}H_{46}NBr$	18.1	18.0	5	20	65	57
43	2-*n*-Hexyl	Cetyl	Br	43–45	$C_{27}H_{50}NBr$	16.4[e]	16.4	5	22	<50	<30
44	4-*n*-Hexyl	*n*-Octyl	Br	[h]	$C_{19}H_{34}NBr$	22.4	22.2	130	14	<50	<30
45	4-*n*-Hexyl	*n*-Decyl	Br	[h]	$C_{21}H_{38}NBr$	20.8	20.7	5	16	80	110
46	4-*n*-Hexyl	Lauryl	Br	99–101	$C_{23}H_{42}NBr$	19.40	19.25	15	18	>100	75
47	4-*n*-Hexyl	Myristyl	Br	36–38	$C_{25}H_{46}NBr$	18.1	18.2	1000	20	55	68
					Heptylpyridine salts						
48	4-*n*-Heptyl	*n*-Octyl	Br	111–113	$C_{20}H_{36}NBr$	21.6	21.5	175	15	<50	50
49	4-*n*-Heptyl	*n*-Decyl	Br	108–110	$C_{22}H_{40}NBr$	20.0	19.9	240	17	180	>200
50	4-*n*-Heptyl	Lauryl	Br	105–108	$C_{24}H_{44}NBr$	18.7	18.6	375	19	120	<50

TABLE I (*Continued*)

No.	R	R^2	X	M.p. °C.[a]	Formula	Halogen, % Calcd.	Halogen, % Obsd.	Soly. in H_2O[b]	Total carbons in R^1 and R^2	Germicidal activity × 10^3[c] *Staph. aureus* 37°	Germicidal activity × 10^3[c] *E. typhosa* 37°
					Octylpyridine salts						
51	4-*n*-Octyl	*n*-Decyl	Br	117–120	$C_{23}H_{42}NBr$	19.35	19.35	425	18	>200	200
					Nonylpyridine salts						
52	2-(2-Methyloctyl)	*n*-Hexyl	Br	46–48	$C_{20}H_{36}NBr$	21.6	22.2	5	15	<50	<30
53	2-(2-Methyloctyl)	*n*-Heptyl	Br	59–61	$C_{21}H_{38}NBr$	20.8	20.8	5	16	50	50
54	2-(2-Methyloctyl)	*n*-Octyl	Br	65–67	$C_{22}H_{40}NBr$	20.0	19.9	5	17	80	105
55	2-(2-Methyloctyl)	*n*-Nonyl	Br	62–64	$C_{23}H_{42}NBr$	19.4	19.4	10	18	140	125
56	2-(2-Methyloctyl)	*n*-Decyl	Br	65–67	$C_{24}H_{44}NBr$	18.7	18.8	30	19	150	>90
57	2-(2-Methyloctyl)	Lauryl	Br	[h]	$C_{26}H_{48}NBr$	17.6	17.6	10	21	50	30
58	4-(2-Methyloctyl)	*n*-Hexyl	Br	Oil	$C_{20}H_{36}NBr$	21.6	21.5	60	15		
59	4-(2-Methyloctyl)	*n*-Heptyl	Br	Oil	$C_{21}H_{38}NBr$	20.8	20.9	150	16	<50	
60	4-(2-Methyloctyl)	*n*-Octyl	Br	Oil	$C_{22}H_{40}NBr$	20.0	20.2	300	17	125	95
61	4-(2-Methyloctyl)	*n*-Nonyl	Br	Oil	$C_{23}H_{42}NBr$	19.4	19.4	400	18	>200	175
62	4-(2-Methyloctyl)	*n*-Decyl	Br	Oil	$C_{24}H_{44}NBr$	18.7	18.8	600	19	110	>90
63	4-(2-Methyloctyl)	Lauryl	Br	Oil	$C_{26}H_{48}NBr$	17.6	17.55	1400	21	180	35
64	4-(5-Nonyl)	*n*-Hexyl	Br	Oil	$C_{20}H_{36}NBr$	21.6	21.6	70	15	<50	<30
65	4-(5-Nonyl)	*n*-Heptyl	Br	Oil	$C_{21}H_{38}NBr$	20.8	20.6	130	16	<50	<30
66	4-(5-Nonyl)	*n*-Octyl	Br	Oil	$C_{22}H_{40}NBr$	20.0	20.0	230	17	<50	<50
67	4-(5-Nonyl)	*n*-Nonyl	Br	Oil	$C_{23}H_{42}NBr$	19.4	19.4	400	18	80	75
68	4-(5-Nonyl)	*n*-Decyl	Br	Oil	$C_{24}H_{44}NBr$	18.7	18.7	600	19	110	80
69	4-(5-Nonyl)	Lauryl	Br	Oil	$C_{26}H_{48}NBr$	17.6	17.6	2000	21	>100	60
70	4-(5-Nonyl)	Myristyl	Br	Oil	$C_{28}H_{52}NBr$	16.6	16.4	>3000	23	50	<50
71	4-*n*-Nonyl	*n*-Heptyl	Br	103–105	$C_{21}H_{38}NBr$	20.8	20.8	200	16		
72	4-*n*-Nonyl	*n*-Octyl	Br	113–115	$C_{22}H_{40}NBr$	20.05	20.05	225	17	160	205
73	4-*n*-Nonyl	*n*-Nonyl	Br	119–120	$C_{23}H_{42}NBr$	19.4	19.4	375	18	180	181
74	4-*n*-Nonyl	*n*-Decyl	Br	65–68	$C_{24}H_{44}NBr$	18.7	18.9	500	19	150	>90
					Undecylpyridine salts						
75	2-*n*-Undecyl	*n*-Amyl	Br	55–58	$C_{21}H_{38}NBr$	20.8	21.2	5	16	110	140
76	2-*n*-Undecyl	*n*-Hexyl	Br	70–72	$C_{22}H_{40}NBr$	20.0	20.0	5	17	165	150
77	2-*n*-Undecyl	*n*-Heptyl	Br	65–68	$C_{23}H_{42}NBr$	19.4	19.7	5	18	>200	>120
78	2-*n*-Undecyl	*n*-Octyl	Br	73–75	$C_{24}H_{44}NBr$	18.75	18.70	5	19	200	130
79	4-*n*-Undecyl	*n*-Butyl	Br	57–59	$C_{20}H_{36}NBr$	21.60	21.65	5	15	70	60
80	4-*n*-Undecyl	*n*-Amyl	Br	62–64	$C_{21}H_{38}NBr$	20.8	21.1	5	16	85	130
81	4-*n*-Undecyl	*n*-Hexyl	Br	81–83	$C_{22}H_{40}NBr$	20.05	19.95	25	17	140	130
82	4-*n*-Undecyl	*n*-Heptyl	Br	102–105	$C_{23}H_{42}NBr$	19.4	19.4	100	18	>200	>200
83	4-*n*-Undecyl	*n*-Octyl	Br	105–107	$C_{24}H_{44}NBr$	18.75	18.95	1000	19	180	170
84	4-*n*-Undecyl	*n*-Decyl	Br	101–104	$C_{26}H_{48}NBr$	17.6	17.6	2000	21	150	70
					Tridecylpyridine salts						
85	2-*n*-Tridecyl	*n*-Butyl	Br	70–71	$C_{22}H_{40}NBr$	20.05	20.4	5	17	170	
86	4-(7-Tridecyl)	*n*-Butyl	Br	Oil	$C_{22}H_{40}NBr$	20.05	20.05	250	17	50	<50
87	4-(7-Tridecyl)	*n*-Hexyl	Br	Oil	$C_{24}H_{44}NBr$	18.75	18.6	350	19	>150	100
88	4-*n*-Tridecyl	Allyl	Cl	64–66	$C_{21}H_{36}NCl$	10.49	10.45	5	16	107	180
89	4-*n*-Tridecyl	*n*-Propyl	Br	62–63	$C_{21}H_{38}NBr$	20.8	20.8	5	16	150	>200
90	4-*n*-Tridecyl	*n*-Butyl	Br	69–70	$C_{22}H_{40}NBr$	20.05	20.05	5	17	>150	115
91	4-*n*-Tridecyl	*n*-Amyl	Br	43–45	$C_{23}H_{42}NBr$	18.55[g]	18.55	5	18	>100	>90
92	4-*n*-Tridecyl	*n*-Hexyl	Br	97–98	$C_{24}H_{44}NBr$	18.75	18.7	20	19	100	>90
93	4-*n*-Tridecyl	*n*-Heptyl	Br	112–114	$C_{25}H_{46}NBr$	18.2	18.2	450	20	<50	<50
					Pentadecylpyridine salts						
94	4-*n*-Pentadecyl	Methyl	Br	113–115	$C_{21}H_{38}NBr$	20.8	20.8	20	16	100	80
95	4-*n*-Pentadecyl	Ethyl	Br	86–88	$C_{22}H_{40}NBr$	20.0	20.0	5	17	100	90
					Heptadecylpyridine salts						
96	4-*n*-Heptadecyl	Methyl	Br	114–116	$C_{23}H_{42}NBr$	19.4	19.3	425	18	<50	<50
97	4-*n*-Heptadecyl	Ethyl	Br	91–93	$C_{24}H_{44}NBr$	18.7	18.7	1600	19	50	30
					Acylpyridine salts						
98	3-Acetyl	Lauryl	Br	110–111	$C_{19}H_{32}NOBr$	21.6	21.4	5	14	<50	<50
99	3-Acetyl	Myristyl	Br	101–103	$C_{21}H_{36}NOBr$	19.2[g]	19.4	5	16	80	140
100	3-Acetyl	Cetyl	Br	65–69	$C_{23}H_{40}NOBr$	18.7	18.8	10	18	70	85
101	3-Valeryl	Lauryl	Br	123–125	$C_{22}H_{38}NOBr$	19.4	19.4	30	17	90	120
102	3-Carbamido	Cetyl	Br	213–216	$C_{22}H_{39}N_2OBr$	18.7	19.2	[i]	[i]	135	80
103	3-Carbethoxy	Myristyl	Br	Oil	$C_{22}H_{38}NO_2Br$	18.6	18.5	5	[i]	75	75

[a] All temperatures are uncorrected. [b] The values indicate the 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. [c] The values given, $\times 10^3$, represent Critical Killing Dilutions. A value of 100, for example, means that the C. K. D. is $1:100 \times 10^3$. 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. [d] Hemihydrate. [e] Monohydrate. [f] Very insoluble. [g] Semisolid. [h] The compound was too hygroscopic for a m.p. determination. [i] Slightly soluble. [j] Total is 18, counting oxygen and nitrogen atoms in line with carbon chain.

TABLE II

REACTION CONDITIONS AND PREPARATION DETAILS

No.[n]	Time,[a] hr.	Temp.,[b] °C.	Reacted, %[c]	Purification method	Recrystn. solvent
1	82	110	90	A	Et_2O
2	67	110	89	A	Et_2O
3	95	110	88	A	Et_2O–acetone
4	48[d]	105	100	A	Acetone
5	48[d]	105	100	A	Et_2O–acetone
6	45	110	94	A	Et_2O–acetone
7	34	135	100	B	Et_2O
8	31	105	96	A	Et_2O
9	117	110	98	A	Et_2O–acetone
10	[e]	110		A	Et_2O–acetone
11	98	95	96	A	Et_2O–acetone
12	48	105	98	A	Et_2O wash
13	49	110	92	A	Et_2O wash
14	50	105	99	A	Et_2O
15	40	110		A	Et_2O–acetone
16	31	105	96	A	Et_2O
17	48	105	97	A	Et_2O wash
18	21	110	100	A	Et_2O wash
19			93	C	Et_2O wash
20	48	105	99	A	Et_2O
21	96	75		A	Et_2O
22	40	110	96	A	Et_2O–acetone
23	31	105	94	A	Et_2O
24	64	105	99	B	Et_2O wash
25	42	110	95	B	Et_2O wash
26	50	110	92	C	Et_2O
27	67	110	100	A	Et_2O
28	75	110	94	A	Et_2O
29	168	80		A	Et_2O wash
30	168	80		A	Et_2O–acetone
31	168	80	95	A	Et_2O–acetone
32	137	110	85	A	Et_2O–acetone
33	49	110	99	A	Et_2O–acetone
34	65	105	100	A	Et_2O wash
35	22	135	93	C	Et_2O–acetone
36	47	110	100	A	Et_2O–acetone
37	48	110		A	Et_2O
38	47	110	100	A	Et_2O
39	44	110	95	A	Et_2O wash
40	67	110	95	B	Et_2O wash
41	70	110		A	Et_2O
42	96	110	93	B	Et_2O–petr. ether
43	70	105	90	A	Acetone, then Et_2O
44	48	110	97	B	Et_2O wash
45	24	110	99	B	Et_2O
46	50	110	100	A	Et_2O–acetone
47	49	110	100	A	Et_2O
48	[f]			C	Et_2O wash
49	[f]			C	Et_2O wash
50	[f]		86	C	Et_2O wash
51	72	75		A	Et_2O–acetone
52	269	80	86	B	Et_2O–abs. Et_2O
53	216	80	96	B	Et_2O–abs. Et_2O
54	72	110		A	Et_2O
55	216	80	93	C	Et_2O
56	216	80	94	B	Et_2O
57	72	110	91	A	Et_2O
58	113	85	91	C	Et_2O wash
59	89	85		A	Abs. Et_2O wash
60	89	85	100	A	Abs. Et_2O wash
61		75		A	Abs. Et_2O wash
62	117	70	95	A	Abs. Et_2O wash
63	123	70	95	A	Abs. Et_2O wash
64	72	80	97	A	Et_2O
65	74	80	100	A	Abs. Et_2O wash
66	80	80	95	A	Et_2O wash
67	144	80		A	Et_2O wash
68	90	80	98	A	Et_2O
69	123	70	98	A	Et_2O wash
70	144	80		A	Et_2O wash
71	68	80		A	Et_2O–acetone
72	66	80		A	Et_2O–acetone
73	66	80		C	Et_2O wash
74	23	75	96	A	Et_2O
75	216	80		A	Et_2O–abs. Et_2O
76	90	65		C	Et_2O–acetone
77	216	80	93	A	Et_2O
78	90	65		A	Et_2O–acetone
79	97	65		C	Et_2O
80	77	85		A	Et_2O–acetone
81	77	85		C	Et_2O
82	72	85	99	C	Et_2O–acetone
83	97	65		A	Et_2O wash
84	72	75		C	Et_2O–acetone
85		60		C	Et_2O–acetone
86	120	75		C	Et_2O wash
87	120	75		C	Et_2O wash
88	[g]			A	Et_2O
89	[h]			C	Et_2O
90		70		C	Et_2O wash
91	40	75	96	C	Et_2O
92	22	75	81	C	Et_2O
93	96	75		C	Et_2O–acetone
94	3 wks.	[i]		C	Et_2O–acetone; acetone
95	168	[i]		A	Butanone; acetone
96[j]	3 wks.	[i]		C	Butanone
97[k]	120	[i]		A	Acetone
98	24	75		A	Et_2O–acetone
99	25	75		A	Et_2O
100	40	75		C	Et_2O
101	48	70		A	Wet Et_2O
102	[l]	70		A	Butanone
103	[m]			B	Et_2O wash

[a] Reaction time. [b] Reaction temperature. [c] Based on determination of ionizable halogen in a weighed sample of the reaction mixture. [d] Methanol solvent for reactants. [e] Several days. [f] 48 hr. at 75°, then 8 hr. at 110°. [g] Room temperature for 6 days, then 20 hr. at 70°. [h] 72 hr. at 80°, then 7 days at 110°. [i] Room temperature. [j] Eleven grams of 4-*n*-heptadecylpyridine and 50 g. of neutralized 25% methyl bromide in methanol were used. [k] A 2-mole excess of ethyl bromide was used. [l] Abs. ethanol solvent. [m] Four days at 75°, then 24 hr. at 110°. [n] The numbers refer to compounds listed in Table I.

distillations of the ether extract yielded 20.5 g. of 3-valerylpyridine; b.p. 106–112° (3.5 mm.), $n^{25}D$ 1.5118.

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

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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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(2) Shelton, *et al.*, THIS JOURNAL, **73**, 3959 (1951).