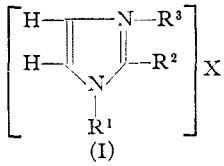
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

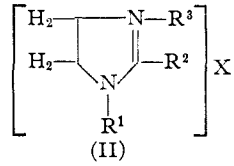
Imidazolium and Imidazolinium Salts as Topical Antiseptics

BY E. R. SHEPARD AND H. A. SHONLE[1]

The general interest in the germicidal action of higher molecular weight quaternary ammonium salts which has followed the introduction of this type of compound into the medicinal field over a decade ago[1a] led us to prepare imidazolium and imidazolinium salts of the structures



(I)



(II)

where R was alkyl or aralkyl and X an anion. In view of the role played by the imidazole group in various biological systems, it was felt that there might be advantages to be gained by incorporating this heterocycle in such molecules as (I) and (II).

Biological evaluation of these salts has shown the expected bacteriostatic effects, the maximum potency being found for those having a C_{12}-C_{14} substituent in the 1 or 2 position of (I) or (II). The bacteriostatic effect roughly paralleled the ability to hemolyze washed red blood cells. However, in the region of lower hemolytic action, *i. e.*, about 2% or less than that of saponin, the bacteri-

TABLE I

Comp. no.	Imidazolium salt	RX used	M. p., °C.	Molecular formula	Nitrogen, % Calcd.	Nitrogen, % Found	Hemolysis, % (Saponin = 100)
1	1,3-Dimethyl-2-heptyl—I	CH_3I	108–109[a]	$C_{12}H_{23}IN_2$	8.69	8.45	
2	1,2-Dimethyl-3-heptyl—I	CH_3I	80–81[a]	$C_{12}H_{23}IN_2$	8.69	8.24	
3	1-Allyl-3-heptyl-2-methyl—Br	C_3H_5Br	Oil	$C_{14}H_{25}BrN_2$			
4	1-Benzyl-2-heptyl-3-methyl—Br	C_7H_7Br	186–187[a]	$C_{18}H_{27}BrN_2$	7.98	7.88	1.6
5	1-(2′,4′-Dichlorobenzyl)-2-heptyl-3-methyl—Cl	$C_7H_5Cl_3$	108–110[b]	$C_{18}H_{25}Cl_3N_2$	7.46	7.42	11.5
6	1-Heptyl-2-methyl-3-benzyl—Cl	C_7H_7Cl	141–142[a]	$C_{18}H_{27}ClN_2$	9.14	9.02	0.96
7	1-Heptyl-2-methyl-3(2′,4′-dichlorobenzyl)—Cl	$C_7H_5Cl_3$	130–131[a]	$C_{18}H_{25}Cl_3N_2$	7.46	7.41	9.0
8	1,3-Dimethyl-2-nonyl—I	CH_3I	127–128[a]	$C_{14}H_{27}IN_2$	8.00	8.01	0.99
9	1-Methyl-2-nonyl-3-ethyl—I	C_2H_5I	81–82[b]	$C_{15}H_{29}IN_2$	7.69	7.57	1.4
10	1-Methyl-2-nonyl-3-allyl—Br	C_3H_5Br	97–98[a]	$C_{16}H_{29}BrN_2$	8.51	8.36	2.3
11	1-Methyl-2-nonyl-3-benzyl—Br	C_7H_7Br	193–195[a]	$C_{20}H_{31}BrN_2$	7.38	7.35	16.0
12	1-Decyl-2,3-dimethyl—I	CH_3I	108–109[b]	$C_{15}H_{29}IN_2$	49.4 7.96	49.3[c] 7.8	4.5
13	1-Decyl-2,3-dimethyl—Br	CH_3Br	83.5–85.5[a]	$C_{15}H_{29}BrN_2$	8.77	8.32	4.5
14	1-Decyl-2-methyl-3-ethyl—Br	C_2H_5Br	Oil	$C_{16}H_{31}BrN_2$			4.0
15	1-Decyl-2-methyl-3-allyl—Br	C_3H_5Br	70–71.5[b]	$C_{17}H_{31}BrN_2$	8.16	8.06	5.2
16	1-Decyl-2-methyl-3-methallyl—Cl	C_4H_7Cl	110–111[d]	$C_{18}H_{33}ClN_2$	8.96	8.93	10.8
17	1-Decyl-2-methyl-3-α-thenyl—Cl	C_5H_5ClS	150–152[a]	$C_{19}H_{31}ClN_2S$	7.91	7.83	
18	1-Decyl-2-methyl-3-benzyl—Cl	C_7H_7Cl	112–114[a]	$C_{21}H_{33}ClN_2$	8.04	7.98	
19	1-Decyl-2-methyl-3-benzyl—Br	C_7H_7Br	87–88[d]	$C_{21}H_{33}BrN_2$	64.1 8.4	64.3[c] 8.32	48.0
20	1-Decyl-2-methyl-3-benzyl—I	C_7H_7I[e]	85.5–87[b]	$C_{21}H_{33}IN_2$	6.36	6.34	26.4
21	1-Decyl-2-methyl-3-(4′-chlorobenzyl)—Cl	$C_7H_6Cl_2$	125–127[d]	$C_{21}H_{32}Cl_2N_2$	7.31	7.05	
22	1,3-Dimethyl-2-undecyl—I	CH_3I	128–130[b]	$C_{16}H_{31}IN_2$	50.8 8.2	50.6[c] 8.2	
23	1-Methyl-2-undecyl-3-methallyl—Cl	C_4H_7Cl	133–134[b]	$C_{19}H_{35}ClN_2$	8.57	8.56	36.0
24	1-Methyl-2-undecyl-3-benzyl—Br	C_7H_7Br	186–187[a]	$C_{22}H_{35}BrN_2$	64.9 8.6	65.0[c] 8.7	377
25	1-Methyl-2-undecyl-3-(4′-nitrobenzyl)—Cl	$C_7H_6ClNO_2$	Oil	$C_{22}H_{34}ClN_3O_2$			
26	1-Amyl-2-undecyl-3-methyl—I	CH_3I	Oil	$C_{20}H_{39}IN_2$			
27	1-Amyl-2-undecyl-3-benzyl—Br	C_7H_7Br	116–117[b]	$C_{26}H_{43}BrN_2$	67.4 9.3	67.3[c] 9.2	804
28	1-Tetradecyl-2,3-dimethyl—I	CH_3I	108–110[b]	$C_{19}H_{37}IN_2$	54.3 8.81	54.2[c] 8.6	322
29	1-Tetradecyl-2-methyl-3-benzyl—Br	C_7H_7Br	102–104[a]	$C_{25}H_{41}BrN_2$	66.8 9.13	66.7 9.3	943

(1) Deceased, February 24, 1947.

(1a) G. Domagk, *Deut. Med. Wochschr.*, **61**, 829 (1935).

TABLE II

Comp. no.	Imidazolinium salt	RX used	M. p., °C.	Molecular formula	Nitrogen, % Calcd.	Nitrogen, % Found	Hemolysis % (saponin = 100)
30	1,3-Dimethyl-2-heptyl—I	CH_3I	46–47[b]	$C_{12}H_{25}IN_2$	8.64	8.59	
31	1-Methyl-2-heptyl-3-(2′-chlorobenzyl)—Br	C_7H_6BrCl	104–105[b]	$C_{18}H_{28}BrClN_2$	7.23	7.14	3.0
32	1-Heptyl-2-methyl-3-benzyl—Br	C_7H_7Br	Oil	$C_{18}H_{29}BrN_2$			
33	1-Benzyl-2-methyl-3-octyl—Br	$C_8H_{17}Br$[f]	56–57[b]	$C_{19}H_{31}BrN_2$	7.63	7.78	3.5
34	1,3-Dimethyl-2-nonyl—I	CH_3I	50–51[b]	$C_{14}H_{29}IN_2$	7.95	7.76	
35	1-Methyl-2-nonyl-3-methallyl—Cl	C_4H_7Cl	Oil	$C_{17}H_{33}ClN_2$			10.0
36	1-Methyl-2-nonyl-3-benzyl—Br	C_7H_7Br	Oil	$C_{20}H_{33}BrN_2$			
37	1-Decyl-2,3-dimethyl—I	CH_3I	103–104[b]	$C_{15}H_{31}IN_2$	49.2 8.47	49.0[c] 8.6	5.2
38	1-Decyl-2-methyl-3-benzyl—Br	C_7H_7Br	74–76[b]	$C_{21}H_{35}BrN_2$	63.8 8.86	63.4 9.08	23.9
39	1-Decyl-2-amyl-3-methyl—I	CH_3I	Oil	$C_{19}H_{39}IN_2$			65.4
40	1-Methyl-2-undecyl-3-benzyl—Br	C_7H_7Br	Oil	$C_{22}H_{37}BrN_2$			
41	1-Amyl-2-undecyl-3-methyl—I	CH_3I	Oil	$C_{20}H_{41}IN_2$			
42	1-Amyl-2-undecyl-3-benzyl—Br	C_7H_6BrCl	Oil	$C_{26}H_{44}BrClN_2$			
43	1-Amyl-2-undecyl-3-(2′-chlorobenzyl)—Br	C_7H_6BrCl	Oil	$C_{26}H_{44}BrClN_2$			
44	1-Dodecyl-2,3-dimethyl—I	CH_3I	120–121[b]	$C_{17}H_{35}IN_2$	51.8 8.9	51.9[c] 9.1	44.3
45	1-Dodecyl-2-methyl-3-benzyl—Br	C_7H_7Br	Oil	$C_{23}H_{39}BrN_2$			
46	1-Dodecyl-2-methyl-3-(4′chlorobenzyl)—Cl	$C_7H_6Cl_2$	Oil	$C_{23}H_{38}Cl_2N_2$			
47	1-Tetradecyl-2,3-dimethyl—I	CH_3I	120–121[b]	$C_{19}H_{39}IN_2$	54.3 8.8	54.5[c] 9.0	446
48	1-Tetradecyl-2-methyl-3-methallyl—Cl	C_4H_7Cl	Oil	$C_{22}H_{43}ClN_2$			
49	1-Tetradecyl-2-methyl-3-benzyl—Br	C_7H_7Br	79–80[b]	$C_{25}H_{43}BrN_2$	66.6 9.5	66.4[c] 9.5	774
50	1-Benzyl-2-methyl-3-octadecyl—Br	$C_{18}H_{37}Br$[g]	90–92[b]	$C_{29}H_{51}BrN_2$	5.53	5.68	

All melting points determined on a Fisher–John's block. [a] Recrystallized from ethyl acetate plus sufficient absolute ethanol to effect solution. [b] Recrystallized from ethyl acetate. [c] Carbon–hydrogen. [d] Recrystallized from ethyl acetate plus sufficient dioxane to effect solution. [e] Reacted at room temperature for half an hour in the presence of ethyl acetate. [f] Twenty hours at 100–110°. [g] Six hours at 100°.

cidal action was considerably diminished even though a fair bacteriostatic activity was maintained. It is interesting to note that the anion had little or no effect on the hemolytic and bacteriostatic effects. Compounds 12 and 29 (Tables I and II) were effective fungistatic agents.

Compounds 12, 14, 15, 19, 27, 29 and 37 have been examined pharmacologically and compared with two commercial quaternary salts—cetyl pyridinium chloride and a mixture of alkyl benzyldimethyl ammonium chlorides. Of these compounds, no. 12 was preferred when skin irritation, effect on cell regeneration, and effect on wounds and burns were considered.

Experimental

The quaternary salts of this series were readily prepared by allowing the appropriate 1,2-disubstituted imidazole or imidazoline to react with an alkyl or aralkyl halide with or without an inert solvent. The reactions were generally not run above 110°, nor were they held at the higher temperatures for too long a time since some decomposition was noted under such conditions. The yields of the imidazolium salts (Table I) and of the imidazolinium salts (Table II) varied from 46 to 97%, and in general yields lower than 90% reflected losses involved in purification. β-Phenylethyl bromide lost hydrogen bromide in the presence of the imidazoles under the conditions reported here to give the hydrobromide of the parent tertiary base.

The following examples illustrate the methods used in obtaining the various salts listed in Tables I and II.

1-Decyl-2,3-dimethylimidazolium Iodide.—A mixture of 44.5 g. (0.2 mole) 1-decyl-2-methylimidazole[2] and 15 ml. (0.24 mole) of methyl iodide in 150 ml. of ethyl acetate was heated in a pressure bottle in a steam-bath for one hour. After cooling, the paste was taken up in an additional 250-ml. quantity of ethyl acetate, filtered, washed and the product recrystallized from 400 ml. of ethyl acetate. The yield was 65.7 g. (90%) of white crystals, m. p. 108–109°.

1-Heptyl-2-methyl-3-benzylimidazolium Chloride.—Three and six-tenths grams of 1-heptyl-2-methylimidazole and 2.8 g. of benzyl chloride were placed in a tube and heated for two hours at 100°. The solid was taken up in 100 ml. of boiling ethyl acetate and 1.5 ml. of absolute alcohol. The solution was filtered and washed with cool ethyl acetate. A second crystallization gave 3.5 g. (57%) of white crystals, m. p. 141–142°.

Acknowledgment.—The authors wish to thank the late Mr. J. T. Bryant for the analyses reported; and H. M. Powell, H. M. Lee and K. K. Chen for the biological and pharmacological studies.

Summary

A series of imidazolium and imidazolinium salts have been prepared and examined for use as topical antiseptics.

INDIANAPOLIS, INDIANA RECEIVED APRIL 12, 1947

(2) The imidazoles and imidazolines used in this work were supplied by the Monsanto Chemical Co., *cf.* U. S. Patent 2,404,299 and 2,404,300.