$$CH_3CH_2NO_2 + HCHO \longrightarrow CH_3CH(CH_2OH)NO_2 \text{ (II)}$$

or

$$H_3CC(CH_2OH)_2NO_2 \longrightarrow II + HCHO$$

These compounds then react according to the mechanism suggested by Henry[1] to give 2-nitro-2,5-dimethyl-4-azahexanol which possesses an amino group $-NH[CH(CH_3)_2]$ and a hydroxyl group on carbon atoms removed by one carbon atom

$$I + II \longrightarrow \begin{matrix} CH_3 & CH_2—NH—CH(CH_3)_2 \\ \diagdown & \diagup \\ C & \\ \diagup & \diagdown \\ NO_2 & CH_2OH \end{matrix} + H_2O$$

III

Inasmuch as amino alcohols with these structural features are known to yield pentoxazolidines with aldehydes, it can be assumed that the final step in any route is the reaction of 2-nitro-2,5-dimethyl-4-azahexanol with formaldehyde to yield water and 5-nitro-3-isopropyl-5-methylpentoxazolidine

$$III + HCHO \longrightarrow \begin{matrix} CH_3 & CH_2—N—CH(CH_3)_2 \\ \diagdown & \diagup \quad \diagdown \\ C & \qquad CH_2 \\ \diagup & \diagdown \quad \diagup \\ NO_2 & CH_2—O \end{matrix} + H_2O$$

The structures chosen for the new compounds are supported by the analytical data. Further confirmation of their structure was obtained by studying the hydrogenation of these compounds and the examination of the reduced products.

An examination of the structures of oxazolidines and pentoxazolidines will reveal that the grouping $=N—\overset{|}{\underset{|}{C}}—O—C—$ is common to both structures. During the hydrogenation of the oxazolidines,[11] the grouping at hand is split as shown

$$=N—\overset{|}{\underset{|}{C}}—O—C + H_2 \longrightarrow =N—\underset{|}{\overset{|}{CH}} + HO—\overset{|}{\underset{|}{C}}$$

A similar splitting of this grouping in the 5-nitropentoxazolidines would be expected to take place if these compounds were hydrogenated. A simultaneous reduction of the nitro group to the amino group should also occur. The hydrogenation of these compounds was tried. The nitrogen content of the product from each of these reductions agreed with that of the expected diamino alcohol. These data furnish additional support for the proposed structures of the 5-nitropentoxazolidines.

Summary

5-Nitropentoxazolidines have been prepared by allowing one mole of a primary amine to react with three moles of formaldehyde and one mole of a primary nitroparaffin.

The hydrogenation of these new compounds was studied. Each nitro compound yielded a new diamino alcohol.

(11) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942); Senkus, *ibid.*, **67**, 1515 (1945).

TERRE HAUTE, IND. RECEIVED OCTOBER 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, JAMES MILLIKIN UNIVERSITY]

Preparation of Symmetrical N,N'-Disubstituted Piperazines and their Quaternary Ammonium Salts

BY D. R. SMITH, J. W. CURRY AND R. L. EIFERT

Domagk,[1] over a decade ago, found that the germicidal activity of quaternary ammonium compounds was increased when a large aliphatic group was attached to the quaternary nitrogen atom. This stimulated the study of the use of quaternary ammonium salts as germicides and, today, many commercial products[2] are on the market. However, only a few quaternary ammonium salts of heterocyclic bases have been tested. Hart and Niederl,[3] recognizing the importance of a cetyl group in bactericidal "invert soaps," prepared N-cetylthiomorpholine and studied several of its derivatives. Shepard and Shonle,[4] investigating topical antiseptics, used imidazole and imidazoline as nuclei and formed quaternary salts with long alkyl chains. Shelton, Van Campen, Tilford, Lang, Nisonger, Bandelin and Rubenkoenig[5] made long chain alkyl quaternary salts using pyridine, picoline, lutidine, piperdine and morpholine and found definite germicidal properties. Later Niederl, Salzberg and Shatynski[6] prepared morpholinium sulfates and found that compounds in the N-hexadecyl series exhibited phenol coefficients of 500 to 600. Baltzly, Buck, Lorz and Schön[7] prepared the one piperazinium salt, containing a long aliphatic chain, that we found in the literature, but it was not tested for germicidal activity. Therefore, it was thought profitable to prepare and test some quaternary ammonium salts of piperazine.

Many N-monosubstituted[7] and N,N'-disubstituted[8] piperazines have been prepared. A new series of *sym*-disubstituted piperazines was first

(1) Domagk, *Deut. Med. Wochschr*, **61**, 829 (1935).
(2) Lesser, *Drug and Cosmetic Ind.*, **64**, 558-560 (1949).
(3) Hart and Niederl, THIS JOURNAL, **66**, 1610 (1944).
(4) Shepard and Shonle, *ibid.*, **69**, 2269 (1947).
(5) Shelton, Van Campen, Tilford, Lang, Nisonger, Bandelin and Rubenkoenig, *ibid.*, **68**, 757 (1946).
(6) Niederl, Salzberg and Shatynski, *ibid.*, **70**, 618 (1948).
(7) Baltzly, Buck, Lorz and Schön, *ibid.*, **66**, 263 (1944).
(8) Forsee and Pollard, *ibid.*, **57**, 1788 (1935).

prepared. These ditertiary amines, with the exception of N,N′-dioctylpiperazine, were white solids, nearly odorless, and with the waxy appearance of the fatty acids. The ditertiary amines were then converted to diquaternary ammonium salts. Since these salts were too insoluble in water to have a practical value, it was thought that a quaternary salt with a sulfate anion might be more soluble. The solubility was only slightly affected, but an emulsifying action, not common to the other salts, was noticed.

Acknowledgments.—The authors wish to express their sincere appreciation to the Research Corporation of New York for a Frederick Gardner Cottrell Grant which made this work possible. They should like to thank Mr. Fred Bandelin of Flint, Eaton, and Company, Decatur, Illinois, for testing these compounds for germicidal activity.

N,N′-DIALKYLPIPERAZINES AND PIPERAZINIUM SALTS

	$R_1 = R_2$	Formula $R_1N(CH_2CH_2)_2NR_2$	M. p., °C. (uncor.)	N Analyses, % Calcd.	Found
1	Octyl	$C_{20}H_{42}N_2$	22–23	9.03	9.05
2	Decyl	$C_{24}H_{50}N_2$	40.5–41	7.65	7.58
3	Lauryl[a]	$C_{28}H_{58}N_2$	48	6.63	6.33
4	Myristyl	$C_{32}H_{66}N_2$	57–58	5.86	5.77
5	Cetyl	$C_{36}H_{74}N_2$	69	5.24	5.22

DIHYDROBROMIDES

				Bromine, %	
6	Octyl	$C_{20}H_{44}N_2Br_2$	307 d.	33.83	33.77
7	Decyl	$C_{24}H_{52}N_2Br_2$	309 d.	30.25	30.40
8	Lauryl	$C_{28}H_{60}N_2Br_2$	306 d.	27.34	27.30
9	Myristyl	$C_{32}H_{68}N_2Br_2$	304 d.	24.95	24.99
10	Cetyl	$C_{36}H_{76}N_2Br_2$	303 d.	22.94	22.93

PIPERAZINIUM SALTS

	R_1	R_2	Formula $[R_1R_2N(CH_2CH_2)_2NR_1R_2]I_2$	M. p., °C. (uncor.)	Nitrogen, % Calcd.	Found
11	Octyl	Methyl	$C_{22}H_{48}N_2I_2$	217 d.	4.72	4.89
12	Decyl	Methyl	$C_{26}H_{56}N_2I_2$	221 d.	4.31	4.34
13	Decyl	Ethyl	$C_{28}H_{60}N_2I_2$	282 d.	4.13	4.04
14	Lauryl	Methyl	$C_{30}H_{64}N_2I_2$	225 d.	3.96	4.04
15	Lauryl	Ethyl	$C_{32}H_{68}N_2I_2$	288 d.	3.82	3.76
16	Myristyl	Methyl	$C_{34}H_{72}N_2I_2$	213 d.	3.68	3.63
17	Myristyl	Ethyl	$C_{36}H_{76}N_2I_2$	273 d.	3.54	3.60
18	Cetyl	Methyl	$C_{38}H_{80}N_2I_2$	213 d.	3.42	3.22
19	Cetyl	Ethyl	$C_{40}H_{84}N_2I_2$	278 d.	3.31	3.26
20	Methyl	Methyl[b]	$C_8H_{20}N_2I_2$	278 d.	..	..
21	Methyl	Ethyl	$C_{10}H_{24}N_2I_2$	240 d.	6.57	6.37
22	Methyl	*n*-Propyl	$C_{12}H_{28}N_2I_2$	227 d.	6.17	6.07
23	Methyl	*n*-Butyl	$C_{14}H_{32}N_2I_2$	213 d.	5.81	5.49
24	Methyl	*n*-Amyl	$C_{16}H_{36}N_2I_2$	202 d.	5.49	5.39
25	Methyl	Phenacyl	$C_{22}H_{28}N_2I_2O_2$	159 d.	4.62	4.45
26	Methyl	Myristyl	$[R_1R_2N(CH_2CH_2)_2NR_1R_2[SO_4R_1]_2$ $C_{36}H_{78}N_2S_2O_8$	255 d.	3.83	3.59

[a] Compound was mentioned by Baltzly, Buck, Lorz and Schön, THIS JOURNAL, 66, 263 (1944), but no constants given. [b] M. p. agreed with that of Abderhalden and Haas, *Z. physiol. Chem.*, 148, 245 (1925).

Experimental

N,N′-Dimethylpiperazine was prepared by methylating piperazine with formic acid and formaldehyde.[9]

N,N′-Diphenacylpiperazine was prepared by the method of Lutz and Shearer[10] which consisted of treating piperazine with phenacyl bromide in alcohol. Sodium carbonate was then added to liberate the amine which was recrystallized from a mixture of alcohol and ethyl acetate.

N,N′-Dialkylpiperazines were prepared by refluxing 0.14 mole of the alkyl halide with 0.06 mole of piperazine hexahydrate in alcohol for twelve to twenty-four hours. The dihydrohalide salts which precipitate can be obtained in 50 to 100% yields, depending on the alkyl halide used. The salt was dissolved in water and converted to the free amine by addition of a 10% solution of sodium hydroxide. The free amines were then recrystallized from methyl or ethyl alcohol with the exception of N,N′-dioctylpiperazine which was purified by vacuum distillation (b. p. 202° at 10 mm.). The yields of the free amines varied from 60 to 90% based on the amount of salt used.

Piperazinium salts were synthesized by refluxing the ditertiary amine with an excess of the appropriate alkyl halide in a small quantity of ethyl alcohol for three to seven hours. The solid precipitating was recrystallized from glacial acetic acid. The yields varied from 30 to 85%. Perhaps better yields could have been obtained in closed vessels. The N,N′-dimyristyl-N,N′-dimethylpiperazinium di-methylsulfate was obtained by treating the tertiary amine with methyl sulfate and refluxing for thirty minutes and recrystallizing the solid obtained from alcohol. Compounds 11, 14 and 18 were also synthesized by refluxing the long chain alkyl halide with N,N′-dimethylpiperazine. The yields obtained were almost the same as by the previous method.

Summary

Four new *sym*-dialkylpiperazines, containing long chain alkyl radicals, and a series of piperazinium salts, derived from *sym*-disubstituted piperazines, have been synthesized.

Compounds 11, 20, 21 and 25, which were tested for germicidal activity against *Staph. aureus*, exhibited no bacteriostatic effect. Other compounds of higher molecular weight than no. 11 were too insoluble to test.

DECATUR, ILLINOIS RECEIVED DECEMBER 23, 1949

(9) Clark, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4576 (1933).

(10) Lutz and Shearer, *J. Org. Chem.*, **12**, 771 (1947).