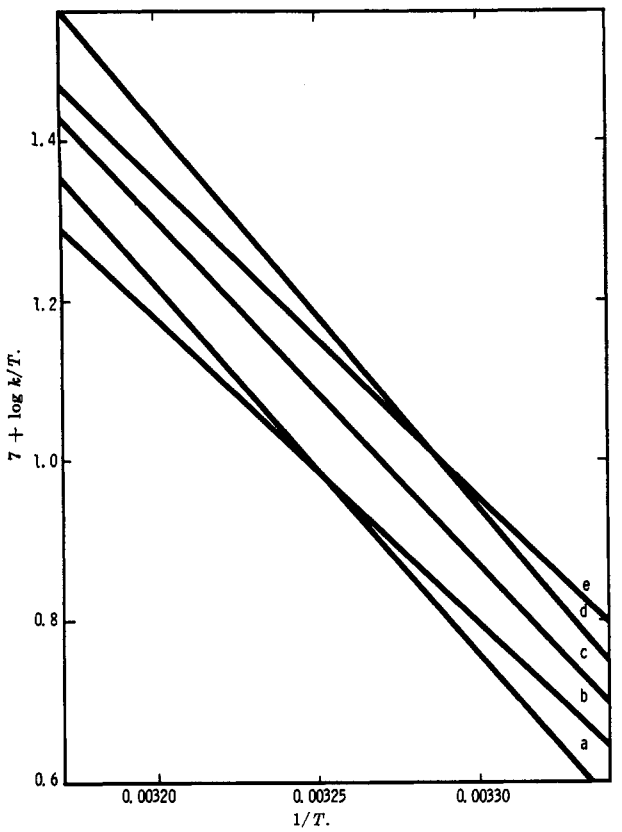

Fig. 3.—Activation plot for data of Table II.

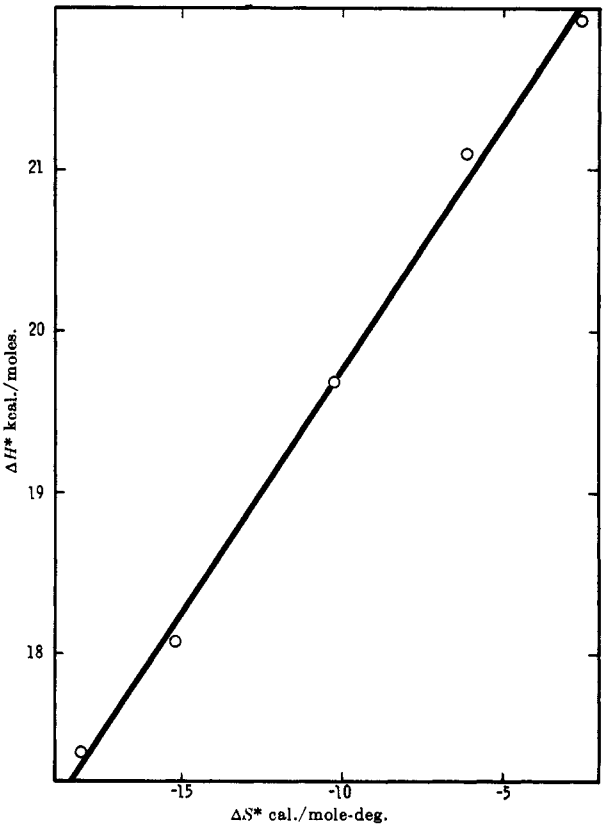

Fig. 4.—Plot of ΔH^* *vs.* ΔS^* for data of Table II.

mental errors, while the ΔH^*–ΔS^* plot has little value for this purpose.

If the iso-kinetic temperature suggested by the ΔH^*–ΔS^* plot does not fall within the range of the measurements, then additional measurements should be made around this suggested temperature.

If the indicated iso-kinetic temperature is not accessible, iso-kinetic temperature for all possible pairs of reactions in the series can be computed and compared (eq. 1 and 2). If these agree well with one another it is reasonable to conclude that an iso-kinetic relationship exists.

In no case can the linear ΔH–ΔS^* plot be taken by itself to be an adequate demonstration of the existence of an iso-kinetic relationship.

The Effect of Axial Alkyl Groups on the Base Strengths of Cyclic Amines

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The pK_a values of 3,3-dimethyl and 3,3,5,5-tetramethyl derivatives of piperidine and N-methylpiperidine were compared with those of the parent amines to determine the effects of 1,3-methyl interactions on pK_a values. Similarly, the pK_a values of 3-azabicyclo[3.2.2]nonane and its N-methyl derivative were compared with those of the corresponding hexamethylenimines to determine the effect of an ethylene bridge. The reductions in pK_a values were all very small and were consistent with a minor polar effect rather than steric hindrance of hydration of the ammonium ions.

An earlier report[1] showed, by pK_a measurements, that secondary ammonium ions are hydrated in solution. The size of the hydrated secondary ammonium ion may be evaluated by determining the extent of its interaction with an axial 3-substituent in a piperidine ring,[2,3] which would lower the pK_a value. Similar substitution in N-methylpiperidine would affect the pK_a value to a lesser extent because tertiary ammonium cations are much less hydrated.[1,4,5]

The possible effects of an ethylene bridge on the pK_a of hexamethyleneimine and N-methylhexamethylene-

(1) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(2) The size of the hydrated *primary* ammonium cation has been determined by two groups: (a) J. Sicher, J. Jonas, and M. Tichy, *Tetrahedron Letters*, 825 (1963); (b) E. L. Eliel, E. W. Della, and T. H. Williams, *ibid.*, 831 (1963).

(3) W. Simon, G. H. Lyssy, A. Moerikofer, and E. Heilbronner ["Collection of Apparent Dissociation Constants in Solvent System Methyl Cellosolve–Water," Juris-Zerlag, Zurich, 1959, p. 62] give a pK_a value of 8.60 for 3,3,5,5-tetramethylpiperidine compared with a value of 9.72 for piperidine, but no details have been given.

(4) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).

(5) J. F. King, in "Technique of Organic Chemistry," Vol. XI, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 342.

TABLE I

SYNTHESES OF INTERMEDIATES AND AMINES

Compd.	Synthesis[a]	Mode of purification	Yield, %	M.p. or b.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Glutaric acid											
2,2-Dimethyl-	*b*	...	...	80.1–82.0							
Amidoglutaric acids											
2,2,4,4-Tetramethyl-	A	Precipitated from water	94.0	159.5–160.5 (bubbles)	$C_9H_{17}O_3N$			7.48			7.43, 7.46
N,2,2,4,4-Pentamethyl-	A	Precipitated from water	97.0	165.0–166.0 (bubbles)[c]	$C_{10}H_{19}O_3N$			6.96			6.90, 6.93
Glutarimides											
2,2-Dimethyl-	B	Added 1 *N* sodium hydroxide solution to crude distillate to bring to pH 7.65, extracted with methylene chloride, evaporated, sublimed at 100° (0.5 mm.)	34.8	145.4–146.9[d]	$C_7H_{11}O_2N$			9.92			9.90, 9.92
N,2,2-Trimethyl-	B	As above; sublimed at 60° (0.2 mm.)	50.1	48.0–50.0	$C_8H_{13}O_2N$			9.03			8.97, 9.02
2,2,4,4-Tetramethyl-	C	Sublimed at 120° (0.40 mm.), recrystallized from heptane–benzene (5:1)	84.7	137.0–139.0	$C_9H_{15}O_2N$	63.88	8.94	8.28	64.14, 63.88	8.85, 8.78	8.46, 8.48
N,2,2,4,4-Pentamethyl-	C	Fractionally distilled	85.7	35.5–38.0; 46–47 (0.20); 93 (5.5)	$C_{10}H_{17}O_2N$	65.54	9.35	7.64	65.40, 65.31	9.23, 9.16	7.53, 7.70
Amines											
3,3-Dimethylpiperidine	D	Fractionally distilled	47.4	135.0–135.8 (atm.)[e]	$C_7H_{15}N$	74.27	13.36[f]		74.67, 74.41, 74.55	13.53, 13.41, 13.23	
3,3,5,5-Tetramethylpiperidine	D	Fractionally distilled	45.9	39.0–41.5; 162.0–165.8 (atm.)[g]	$C_9H_{19}N$	76.52	13.56		76.50, 76.50	13.72, 13.73	
3-Azabicyclo[3.2.2]nonane	[h]	Sublimed at 100° (20 mm.),	...	187.0–188.0							
Hexamethylenimine	[i]	Dried over potassium hydroxide pellets, fractionally distilled	...	136 (atm.)							
N,3,3-Trimethylpiperidine	D	Fractionally distilled	39.8	132.0–134.5 (atm.)[j]	$C_8H_{17}N$	75.52	13.47[k]		75.65, 75.63	13.35, 13.21	
N,3,3,5,5-Pentamethylpiperidine	D	Fractionally distilled	43.6	156.7–159.2 (atm.)[l]	$C_{10}H_{21}N$	77.35	13.63		76.96, 77.04	13.76, 13.81	
N-Methyl-3-azabicyclo[3.2.2]nonane	E	Fractionally distilled	68.1	104 (69); 84 (28)[m]	$C_9H_{17}N$	77.63	12.31[n]		77.3, 76.8	12.51, 12.20	
N-Methylhexamethyleneimine	E	Treated with benzenesulfonyl chloride, dried, fractionally distilled	48.5	137.0–137.5 (atm.)[o]	$C_7H_{15}N$	74.3	13.4		74.1	13.3	

[a] Letters refer to procedures described in Experimental. [b] Source, Aldrich Chemical Co. [c] With 2,2,4,4-tetramethyl acid, m.m.p. 147–149° (bubbles). [d] E. E. Blaise [*Bull. soc. chim. France*, [3]**21**, 628 (1899)] and D. Hoch and P. Karrer [*Helv. Chim. Acta*, **37**, 397 (1954)] report m.p. 150°. [e] V.p.c. purity, 99+%; $n^{25}D$ 1.4455. Hoch and Karrer[d] report b.p. 136–138°, and R. C. Schreyer [*J. Chem. Soc.*, **74**, 3194 (1952)] reports b.p. 45–46° (33 mm.), $n^{25}D$ 1.4470. [f] Neut. equiv.: calcd., 113.2; found, 110.9 and 113.9. [g] V.p.c. purity, 98+%. [h] Source, Eastman Kodak Co. [i] Source, Du Pont. [j] V.p.c. purity, 99+%; $n^{25}D$ 1.4360. [k] Neut. equiv.: calcd., 127.2; found, 130.8 and 128.2. [l] V.p.c. purity, 98+%. [m] V.p.c. purity, 99+%; $n^{25}D$ 1.4892. [n] Neut. equiv.: calcd., 139.2; found 139.2 and 140.0. [o] V.p.c. purity, 99+%; R. Lukes and J. Malek [*Collection Czech. Chem. Commun.*, **16**, 23 (1957)] report b.p. 138.8–140.0°.

imine were also of interest in this connection. The structures, in Fig. 1, are undergoing rapid change because of chair–chair interconversions, the nitrogen inversion phenomenon in the free amines, and the exchange of hydrogens on nitrogen. Therefore, the effect of structural alterations on pK_a must be an average effect on a mobile system.

Results

3,3-Dimethylpiperidine, 3,3,5,5-tetramethylpiperidine, and their N-methyl derivatives were synthesized by conventional reactions (Fig. 2 and Table I). N-Methyl-3-azabicyclo[3.2.2]nonane was prepared from commercially available 3-azabicyclo[3.2.2]nonane. The pK_a values in water at 30.0° of all amines were determined by potentiometric titration and the results are given in Table II.

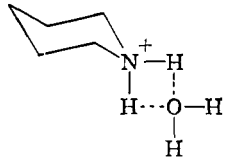
The effect of the axial groups is small in every case. In piperidine and N-methylpiperidine, the 1,3-diaxial methyl groups lower the pK_a value by 0.9 and 0.7 units, respectively; a single axial methyl group shows intermediate behavior. Introduction of an ethylene bridge into hexamethyleneimine and N-methylhexamethyleneimine lowers pK_a by 0.3 and 0.1 units, respectively.

Discussion

Tertiary Amines.—The N-methyl group, equatorial in the piperidines and probably similar in the hexamethyleneimine derivatives, will assume the same position in the corresponding cations.[6] The problem does not arise for N-methyl-3-azabicyclo[3.2.2]nonane because it is symmetrical. Accordingly, conformational isomerism of the methyl group does not affect the pK_a values. The slight downward trend seen in Table II is attributed to a slight electron-withdrawing field effect of the 3- and 5-methyl groups in the alicyclic systems.[7] This contrasts with the normal electron-donating inductive effect of the methyl groups at the closer 2- and 6-positions.[8]

Secondary Amines.—Again the polar factor causes the mild decline in pK_a with increasing methyl substitution. The secondary amines are stronger bases than the tertiary amines by 0.6 ± 0.1 pK_a unit, in fair agreement with an earlier[1] value of 1.1 pK_a unit for a wider variety of amines. The constancy of this difference speaks against significant steric hindrance of solvation of the secondary ammonium ions.

The water molecule(s) are bonded to two hydrogens on nitrogen in the cation[1] and are few in number because small in size. Perhaps a structure such as the following contributes heavily to the averaged system. This accords with the interpretation of Yerger and



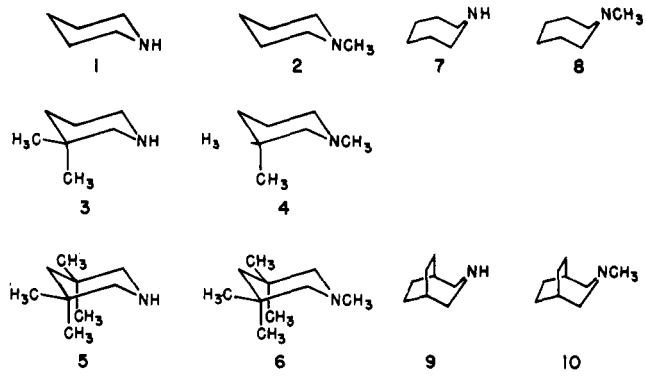


Figure 1.

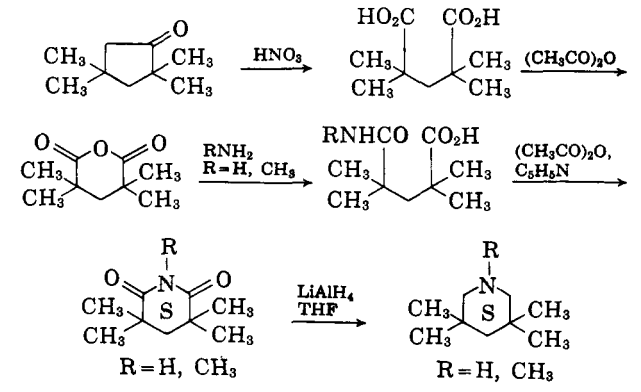


Figure 2.

Barrow[9] of the infrared spectra of secondary ammonium ions solvated by carboxylate ion in carbon tetrachloride.

Experimental

2,2,4,4-Tetramethyladipic Acid.—Nitric acid oxidation of 3,3,5,5-tetramethylcyclohexanone gave 2,2,4,4-tetramethyladipic acid.[10] The cyclic anhydride was incidentally prepared as follows. Acetic acid (18 ml., b.p. 118°) was distilled in a spinning-band column from a mixture of 26.8 g. (0.133 mole) of 2,2,4,4-tetramethyladipic acid and 50 ml. of acetic anhydride. The residue was distilled in a Claisen flask at 150 mm. with a pale blue flame. The yellow semisolid distillate was redistilled at atmospheric pressure, taken up in ether, washed with 10% sodium carbonate solution, dried over magnesium sulfate, and distilled in a spinning-band column. The anhydride, b.p. 146–162° (31 mm.), 15.44 g. (63.0%), crystallized in the receiver; m.p. 38.0–41.8°. The infrared spectrum was satisfactory for a cyclic anhydride.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92 and 64.95; H, 8.33 and 8.20.

2,2,4,4-Tetramethylcyclopentanone.—Cyclization of 2,2,4,4-tetramethyladipic acid by distillation from barium oxide gave 2,2,4,4-tetramethylcyclopentanone.[10,11] 2,2,4,4-Tetramethylglutaric anhydride (b.p. 252°, m.p. 90.5–91.5°), identical with that prepared below, was formed as a by-product.

2,2,4,4-Tetramethylglutaric Acid.—Nitric acid oxidation[12] of 2,2,4,4-tetramethylcyclopentanone gave a 74% yield of 2,2,4,4-tetramethylglutaric acid, m.p. 193.0–194.0°, from water (lit. m.p. 186°,[13] 192°[14]).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.6. Found: C, 57.6; H, 8.6.

(6) G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959).

(7) (a) H. Kwart and L. I. Miller, *ibid.*, **83**, 4552 (1961); (b) H. Kwart and T. Takeshita, *ibid.*, **84**, 2833 (1962).

(8) H. K. Hall, Jr., *ibid.*, **79**, 5444 (1957).

(9) E. A. Yerger and G. M. Barrow, *ibid.*, **77**, 4474 (1955).

(10) G. Slomp, Jr., M. Inatome, C. E. Bowers, J. M. Derfer, K. W. Greenlee, and C. E. Boord, *J. Org. Chem.*, **25**, 514 (1960).

(11) C. Sandris and G. Ourisson, *Bull. soc. chim. France*, 958 (1958).

(12) This experiment was done by Dr. F. B. Moody.

(13) J. Michailenko and W. Jaworski, *J. Russ. Phys. Chem. Soc.*, **32**, 328 (1900); *Chem. Zentr.*, **71**, 529 (1900).

(14) O. Aschan, *Ann.*, **387**, 83 (1912).

TABLE II
pK_a VALUES[a]

Amine	Initial concn., $M \times 10^3$	pK_a
Tertiary amines		
N-Methylhexamethyleneimine	32.3, 1.35	10.38, 10.22
N-Methyl-3-azabicyclo[3.2.2]nonane	3.82, 2.17	10.24, 10.23
N-Methylpiperidine	...	10.08[b,c]
N,3,3-Trimethylpiperidine	1.25, 5.19, 1.91, 1.75	9.62, 9.87, 9.80, 9.80
N,3,3,5,5-Pentamethylpiperidine	0.604, 0.565	9.44, 9.42
Secondary amines		
Piperidine	35.5, ...	10.98, 11.05[c]
Hexamethyleneimine	36.1	10.93
3-Azabicyclo[3.2.2]nonane	36.1, 28.0	10.56, 10.58[b]
3,3-Dimethylpiperidine	7.07, 7.48	10.38, 10.39
3,3,5,5-Tetramethylpiperidine	2.57, 2.56	10.15, 10.06

[a] In water at 30.0°. [b] At 25.0°. [c] See ref. 18.

2,2,4,4-Tetramethylglutaric Anhydride.—The anhydride was prepared from the acid using acetic anhydride as above.[15] Two recrystallizations from hexane gave an 82% yield, m.p. 88–91° (lit.[14] m.p. 86–87°). The infrared spectrum showed absorption from a cyclic anhydride at 5.58 and 5.70 μ.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.5; H, 8.29; O, 28.20. Found: C, 63.7; H, 8.2; O, 28.3.

Procedure A. Amido-3,3,5,5-tetramethylglutaric Acids.—Into a stirred, chilled mixture of 20 ml. of 28% ammonium hydroxide, 50 ml. of water, and 70 ml. of acetone was added in small portions over 30 min. 15.0 g. (0.088 mole) of 2,2,4,4-tetramethylglutaric anhydride. The mixture was stirred 20 min. more, taken to dryness under vacuum on a rotating evaporator, taken up in 70 ml. of water, and acidified with 15 ml. of 36% hydrochloric acid. The crystalline precipitate which formed was filtered, rinsed with water, and dried to give 15.5 g. of 2,2,4,4-tetramethylglutaramic acid.

Procedure B. 3,3-Dimethylglutarimides.—The procedure was that of Grogan and Rice.[16] The yields were lower than in procedure A followed by C, but difficulties caused by ring opening at two different carbonyl groups were avoided.

Procedure C. 2,2,4,4-Tetramethylglutarimides.—A mixture of 11.82 g. (0.0631 mole) of 2,2,4,4-tetramethylglutaramic acid and 7.08 g. of acetic anhydride in 47.5 ml. of pyridine was heated to boiling for 1 min. and was then set aside at room temperature for 17.5 hr. It was poured into a mixture of 50 ml. of 36% hydrochloric acid and 100 g. of ice and shaken vigorously. The mixture was extracted four times with chloroform. The organic layer was dried over magnesium sulfate, evaporated, and sublimed at 120° (0.4 mm.), to give 9.83 g. of white solid. This was recrystallized from a mixture of 40 ml. of heptane and 8 ml. of benzene to give 9.66 g. of 2,2,4,4-tetramethylglutarimide.

Procedure D. Amines.—In a typical experiment, to a refluxing solution of 8.31 g. (0.219 mole) of lithium aluminum hydride in 100 ml. of purified tetrahydrofuran was added with stirring over 2.5 hr. a solution of 14.7 g. (0.104 moles) of 2,2-dimethylglutarimide in 210 ml. of tetrahydrofuran. Stirring and refluxing were continued for 68 hr. The mixture was chilled and, with stirring, a solution of 50 g. of sodium hydroxide in 50 ml. of water was added. Tetrahydrofuran was distilled with stirring and the residue was steam distilled until the distillate was no longer strongly basic. The total distillate was acidified with 15 ml. of 36% hydrochloric acid and evaporated to dryness. The residue was taken up in 60 ml. of water, basified with 15 ml. of 50% sodium hydroxide, and extracted with three 100-ml. portions of ether. The ether was distilled and the residue was dried over magnesium sulfate and then distilled under nitrogen from sodium hydride or sodium in a small spinning-band column. 3,3-Dimethylpiperidine, 5.60 g., boiled at 135.0–135.8°.

Procedure E. N-Methylation of Amines.—The procedure was that of Cohen and Minsk.[17]

pK_a Determinations.—The pK_a values were determined by potentiometric titration at constant temperature, using degassed distilled water as solvent and 0.1 N hydrochloric acid as titrant.[18] The amine, 0.2–5.0 mequiv., was dissolved with magnetic stirring in 200.0 ml. of degassed distilled water in a stoppered flask. The solution was carefully checked for homogeneity. It was transferred to a 500-ml., five-necked flask immersed in a 30.0° bath. Titration was performed under a quiet nitrogen blanket using a Gilmont 10-ml. pipet. Motor-driven stirring was provided before each reading. Twelve points were taken during the main part of the titration and numerous points to define the equivalence point. The pK_a values were calculated from the twelve points using the given equation.[18] The over-all average of the standard deviations within each determination of pK_a values was ± 0.02 units. The values were reproducible to 0.1 pK unit, indicated in Table II, except in one unexplained instance. Two pK_a values for N-methyl-3-azabicyclo[3.2.2]-nonane of 9.77 and 9.77 were obtained, which could not be duplicated later. The initial concentration of amine had a very small effect on the pK_a value. Thus, at the low concentration of 0.00408 M, N,2,2,6,6-pentamethylpiperidine[8] gave a pK_a value of 10.98 ± 0.03 compared with an earlier value of 11.25, obtained at higher concentration.

N.m.r. Spectra.—The n.m.r. spectra were determined on a Varian A-60 spectrometer. The amines were studied as carbon tetrachloride solutions, first as such and then with a drop of D_2O added. The spectra of the cations were obtained using solutions of the amines in trifluoroacetic acid solution, which appeared to be stable for several days. Tetramethylsilane was used as an internal standard. The spectra agreed with the assigned structures. No distinction between axial and equatorial methyl groups was observed.

Infrared Spectra.—As expected from the work of Bohlmann,[19] the N-methylamines absorbed at 2600–2800 cm.$^{-1}$ because they all possessed two hydrogen atoms *trans* coplanar to the lone-pair electrons.

Acknowledgment.—The author is deeply indebted to Mrs. Janet Willoughby, Mr. J. F. Grezlikowski, Jr., and Mr. P. Baiocco for excellent technical assistance, to Dr. F. B. Moody and Dr. D. R. Wilson for permission to quote their unpublished experiments, to Dr. J. A. Snyder for a sample of N-methyl-3-azabicyclo[3.3.2]-nonane, and to a referee for helpful comments.

(15) This experiment was done by Dr. D. R. Wilson.
(16) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).
(17) H. L. Cohen and L. M. Minsk, *J. Am. Chem. Soc.*, **79**, 1762 (1957).
(18) S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *ibid.*, **78**, 4917 (1956).
(19) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).