The Nuclear Magnetic Resonance Spectra of Some N-Substituted Methylamines. II. Effect of Acidic Conditions

MORRIS FREIFELDER,[1] RICHARD W. MATTOON, AND R. W. KRIESE

Organic Chemistry Department and Chemical Physics Laboratory, Research Division, Abbott Laboratories, North Chicago, Illinois

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The nmr spectra of a number of N-substituted methylamines in acidic media are examined. Among those studied—$RNHCH_3$ (R is alkyl, aralkyl, cyclic, or cycloalkyl)—the N-methyl signal is a triplet (J = 5.5 cps) when the spectra are run in various solvents to which hydrochloric acid is added to pH 1.0 or below. Under similar conditions the spectra of tertiary N-methylamines, where one of the above R groups is substituted for hydrogen, show the N-methyl signal as a doublet (J = 4–5.5 cps). Splitting of the signal among saturated N-methyl heterocycles is observed in strongly acidified solvent only when one nitrogen atom is part of the heterocyclic system. In neutral solvent, the spectra of the aforementioned compounds show a single peak for the N-methyl protons in every instance. In the piperazine series, if one ring nitrogen is acylated and the spectrum of the 1-acyl-4-methylpiperazine is run in trifluoroacetic acid (TFA), the N-methyl signal is seen as a doublet, otherwise a single peak is noted among other N-methylpiperazines. An attempt is made to classify N-substituted methylamines by means of the N-methyl signal in their spectra in neutral solvent and various acidic media.

In the nmr spectra of a number of N-substituted methylamines—$RNHCH_3$, where R was an aryl, aralkyl, or alicyclic group—the signal for the N-methyl protons was a singlet.[2] In the same study splitting of the signal was noted when the $-NHCH_3$ group was adjacent to a carbon atom joined by a double bond to a heteroatom, *e.g.*, $RC(=S)NHCH_3$. This suggested that decreasing the basicity of the nitrogen might have been instrumental in affecting the rate of exchange so that the split signal could be observed.[3] This effect of changing the basicity of the nitrogen was further emphasized when a doublet for the N-methyl protons was seen among some N-methylsulfonamides, RSO_2NHCH_3, where the proton on nitrogen is definitely acidic.[2]

These results made it appear worthwhile to examine the effect of an acid environment on the N-methyl signal in the spectra of a number of N-substituted methylamines.[4] It was our purpose to determine whether it would be possible to classify N-substituted methylamines by their nmr spectra in neutral and acidic media.

Experimental Section

The spectra were run in pure solvents at a 10–20% concentration in a Varian A-60 spectrometer at 32–33° at a sweep width of 500 cps with tetramethylsilane (TMS) as internal standard. When TFA was used, TMS was sealed in a capillary tube. Sodium 3-trimethylsilyl-1-propanesulfonate was the standard for spectra run in aqueous solution. The usual procedure was to run the sample in the appropriate solvent, record, and integrate the entire spectrum.[5] Concentrated hydrochloric acid was added to the solution to at least pH 1.0 and the spectrum was again recorded (other mineral acids may also be satisfactory). When precipitation of the hydrochloride salt took place, the spectrum was rerun in water acidified to the same pH. If splitting of the signal did not occur, the spectrum of a solution of the base in concentrated hydrochloric acid was examined in a few cases. In general, TFA was the solvent employed for those amines which continued to show a single peak for the N-methyl signal.[6]

Only those signals which have some bearing on this study are recorded in Tables I–III or in the accompanying footnotes. Most of the compounds are reported in the literature; a number are commercially available. Many were generously supplied by colleagues in this laboratory to whom the authors are most grateful. Thanks are also due to Mrs. Ruth Stanaszek for running most of the spectra.

TABLE I

SECONDARY AMINES

$RNHCH_3$

Compd	R	Solvent[a]	—N-Methyl protons, cps— b	c
I	C_6H_5	A		189.5
		B		192
II	$4\text{-}CH_3C_6H_4$[d]	A		193
		B		192 (broad)
III	C_6H_{11}	C	140.5	157, 163, 168.5
		D	137.5	151, 156.5, 162
IV	$C_6H_5CH_2$[e]	D	137	155.5, 161, 166.5
		E	138.5	153.5, 159, 164.5
V	$2\text{-}CH_3OC_6H_4CH_2$[f]	E	140	164.5, 170, 175.5
		F[g]		163, 169, 174
VI	$C_6H_5CHOHCH(CH_3)$	F	169[h]	163.5, 169.5, 175
VII	H_3C	D	136.5	170, 176, 181.5

[a] A, trifluoroacetic acid; B, concentrated hydrochloric acid; C, no solvent; D, deuterated dimethyl sulfoxide; E, carbon tetrachloride; and F, water. [b] Peak position before addition of acid. [c] Peak position after addition of concentrated hydrochloric acid to pH 1.0 or below. [d] The signal for the $4\text{-}CH_3$ protons is seen at 141 cps in A and 141.5 cps in B. [e] The side-chain methylene proton signal is a singlet at 216.5 cps in D and 218.5 cps in E. These signals become triplets upon the addition of acid at 242, 247.5, and 253 and 247.5, 253.5, and 259 cps, respectively. [f] The methoxy signal is at 224 cps and the methylene signal at 196 cps in E. Addition of acid moves the methoxy signal to 239 cps, while the methylene signal becomes a triplet: 252, 258, and 264 cps. [g] The compound was dissolved in dilute hydrochloric acid. [h] The hydrochloride salt was used; the pH of the solution was about 6.5.

Results and Discussion

The N-methyl signal for compounds I and II was a singlet in each spectrum in concentrated hydro-

(1) To whom inquiries should be addressed.

(2) M. Freifelder, R. W. Mattoon, and R. Kriese, *J. Phys. Chem.*, **69**, 3645 (1965).

(3) J. C. N. Ma and E. W. Warnhoff [*Can. J. Chem.*, **43**, 1849 (1965)] reported a singlet for the methyl protons in N-methylurea in deuteriochloroform at 38°. In our hands the signal was a doublet (J = 4.5 cps) in carbon tetrachloride at 33°.[2]

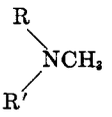
(4) The appearance of the work of J. J. Hedberg, J. A. Weil, G. A. Janusonis, and J. K. Anderson [*J. Phys. Chem.*, **41**, 1033 (1964)], who reported splitting of the N-methyl signal among dinitro- and trinitro-N-methylanilines, gave added impetus to this study.

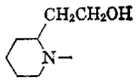
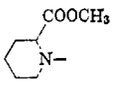
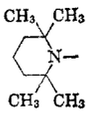
(5) An additional sample was treated with D_2O to note exchangeable protons.

(6) While this work was being completed Ma and Warnhoff[3] reported on the use of nmr spectroscopy for the detection, characterization, and estimation of N-methyl groups. Some of the compounds in their publication are also covered in our study. They routinely used TFA to cause splitting of the N-methyl signal. In this investigation TFA was used as a last resort. The use of organic solvent and acid is much less expensive and far more revealing. Selective splitting of the N-methyl signal resulting from their use enabled us to classify certain N-methylamines.

TABLE II

TERTIARY AMINES

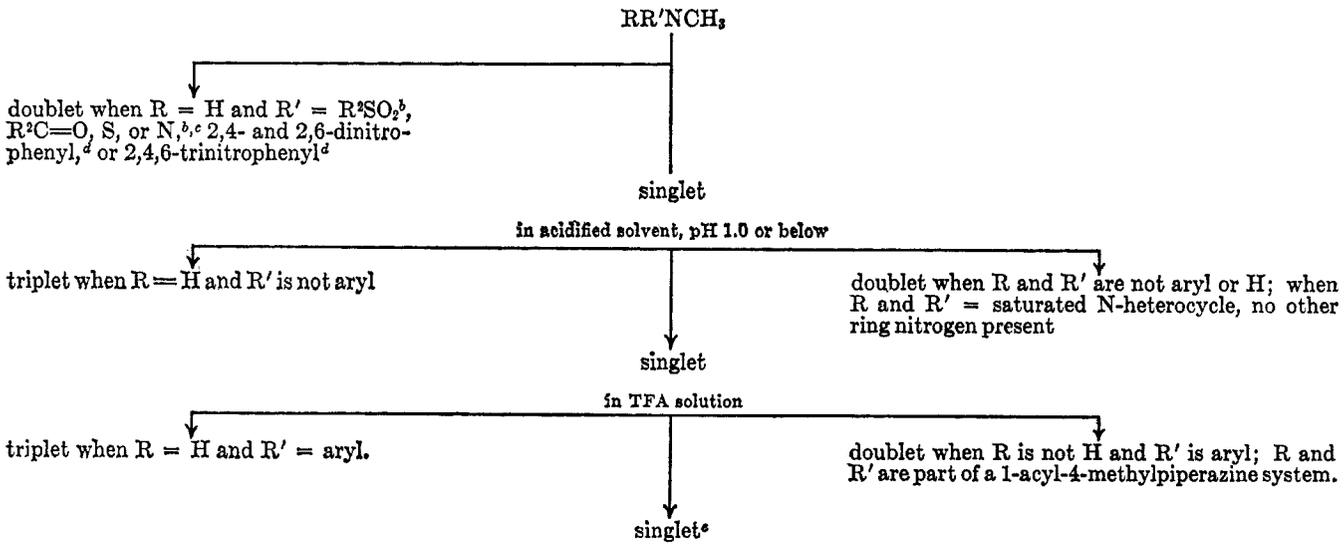


Compd	R	R′	Solvent[a]	Peak Positions, cps: b	Peak Positions, cps: c
VIII	$C_6H_5CH_2$[d]	CH_3	A	129	173.5, 177.5
IX	$C_6H_5CH_2CH(CH_3)$[e]	CH_3	A	132	170.5, 175.5
X	$C_5H_{10}NCC(C_6H_5)_2CH_2$[f] (O)	CH_3	B	157	153, 157.5
XI	$(C_6H_5)_2C(OH)CH_2NH(CH_2)_3$[g]	CH_3	B	183	177, 182
XII	CH_3[h]	CH_3	B		172, 177
XIII	C_6H_{11}	C_6H_{11}	B		161, 166.5
XIV	[i]		B	169.5	168, 173.5
XV			B		171.5, 177
XVI			B		173.5, 178.5
XVII[j]			B		165, 170
XVIII			B		173.5, 178.5

[a] A, deuterated dimethyl sulfoxide; B, water. [b] N-Methyl proton signal before addition of acid. [c] N-Methyl proton signal after addition of concentrated hydrochloric acid to pH 1.0 or below. [d] The methylene proton signal is a singlet at 202.5 cps. After addition of acid it becomes a doublet, 267.5 and 272 cps. In acidic aqueous solution (pH 1.0) it is a doublet at 259 and 264.5 cps and the N-methyl signal is seen at 172.5 and 177.5 cps. [e] The methyl protons signal in the side chain was first a doublet, 47.5 and 54 cps, which moved downfield to 66.5 and 73 cps after the addition of acid. Much splitting was noted in the signals of the other side-chain protons further downfield. [f] Run as the hydrochloride salt; pH of solution was 6.5. [g] Run as dihydrochloride salt; pH of solution was 5.5. [h] Solution of hydrochloride salt acidified to pH 1.0. [i] Compound XIV has the following structure: $C_6H_{11}N(CH_3)$–$(CH_2)_8$–$N(CH_3)$-$C_6H_{11}\cdot 2HCl$; pH of aqueous solution was about 6.5. [j] The spectrum of the acidic solution showed two methyl signals at 83.5 and 86 cps, respectively.

SCHEME I

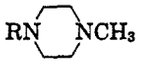
THE N-METHYL SIGNAL IN THE SPECTRA OF N-SUBSTITUTED METHYLAMINES[a]



[a] The classification is based on examination of the spectra of the free bases in neutral solvent (pyridine was used, see ref 2). In aqueous solution the signal is a singlet. [b] R^2 = any group or H. [c] No amidines were available to us. Among the guanidines, doublets were noted. [d] There are no reports except ref 5 concerning polynitro-N-methylanilines. [e] The remainder should include other tertiary N-methylamines.

TABLE III

N-METHYLPIPERAZINES



Compd	R	Solvent[a]	N-Methyl protons, cps
XIX	H_3C	A	184
XX	H_3COOC	A	178[b]
XXI	H_5C_6	A	180.5
XXII	$H_{11}C_6$	A	185
XXIII	2-ClH_4C_6	A	192
		B	195
		C	198[c]
	C_6H_{11}	B	184
XXIV	$(C_6H_5)_2C(OH)CH(CH_3)$–	C	183[d]
XXV	$C_6H_{11}C(OH)CH_2(C_6H_5)$–	C	182[e]
		D	136[f]
XXVI	HC(=O)–	A	179
XXVII	C_6H_5C(=O)–	C	187, 192[g]
		A	177.5
		E	203
		C	185.5, 190
XXVIII	*h*	D	*i*
		A	*j*
		C	*k*

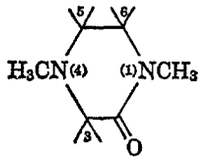
[a] A, water plus concentrated hydrochloric acid to pH 1.0; B, concentrated hydrochloric acid; C, trifluoroacetic acid; D, D_2O; and E, deuterated dimethyl sulfoxide plus concentrated hydrochloric acid. [b] Signal for the $COOCH_3$ protons is at 225 cps. [c] At 60° the signal is a singlet at 193 cps, at 0° the signal is at 199 cps. [d] The methine signal is very complex. It appears to be a quartet centered at 288 cps with much fine splitting. [e] The methylene proton signal is seen at 233 cps in the midst of the methylene protons of the piperazine ring (integration, 10 H). The ratio of this group to the N-methyl signal is 10.1:3. [f] The O=C*H* signal is at 479 cps; the pair of methylene protons adjacent to the formyl-substituted nitrogen are farther downfield than the other pair: one is centered at 210 cps, the other at 152 cps. These signals are typical of an A_2B_2 system. [g] The O=C*H* is now at 498 cps. [h] 1,4-Dimethyl-2-ketopiperazine. [i] The 1-CH_3 signal is at 177 cps; the 4-CH_3 signal is at 140 cps. In carbon tetrachloride the 4-CH_3 signal is at 136 cps and the 1-CH_3 signal is at 172 cps. [j] Two separate peaks at 182 and 184 cps. [k] Two separate peaks at 192 and 194 cps.

chloric acid and in TFA.[7] Among the more basic secondary amines the N-methyl signal was a triplet in the spectra in acidified solvent (compounds III–VII, Table I). Under similar conditions the signal was a doublet in the spectra of the tertiary amines $RR'NCH_3$, where R and R′ are similar or different alkyl, aralkyl, or alicyclic groups or where R and R′ are part of a saturated heterocyclic system containing no other N atom (compounds VIII–XVIII, Table II).

The change of the methylene signal of IV and V from a single peak to a triplet in the spectra in aqueous acid and the change in the methine signal of VI and also IX to a complex multiplet in the same solvent is in agreement with Ma and Warnhoff's findings in TFA.[3]

(7) W. F. Reynolds and T. Schaefer [*Can. J. Chem.*, **41**, 2339 (1963)] report a triplet ($J \cong 5.5$ cps) for the signal of I in TFA. They state that the exchange rate is a function of temperature and concentration and are investigating this. In our hands the inability to keep concentrated solutions of the amines from precipitating may be one of the reasons that only a single peak was recorded. Ma and Warnhoff[3] reported a broad unresolved area in the spectrum in TFA at 38° but a triplet at 27°.

In the piperazine series splitting of the N-methyl signal was observed only when the spectra of 1-acyl-4-methylpiperazines were run in TFA. When the same were run in dilute aqueous or concentrated hydrochloric acid the signal reverted to a singlet, owing probably to the presence of water. The spectra of 1,4-dimethyl-2-ketopiperazine are of interest. In carbon



tetrachloride two methyl signals are noted at 135.5 and 172.5 cps. The peak downfield is assigned as the 1-methyl signal,[8] leaving the peak for the methyl protons of the more basic nitrogen upfield. The C-6 signal is a broad based triplet centered at 198 cps (J = 6 cps) with some fine splitting. The C-5 signal is a similar triplet centered at 154 cps (J = 6 cps). The two signals are characteristic of an A_2B_2 system. The C-3 signal is a peak at 177 cps, but it cannot be integrated separately from the 1-methyl signal. Integration of the two is very exact (5 H) as is the integration of the other signals—4-CH_3 (3 H), C-5 (2 H), and C-6 (2 H). When the spectrum is run in TFA there is evidence of protonation—the methylene signals broaden and lose resolution—but splitting of the methyl signals does not take place. The methyl peaks did shift to 192 and 194 cps, but individual assignments were not made. In aqueous hydrochloric acid the two methyl peaks are found as singlets at 182 and 184 cps. A doublet at 239 and 244 cps may be the signal for the C-3 protons (originally a singlet in carbon tetrachloride) since it integrates to 2 H compared with an area (4 H), a multiplet centered at 223 cps, assumed to be the C-5 and C-6 signals. The striking shift downfield of both the C-3 and C-5 signals by more than 60 cps and the 4-CH_3 signal by almost 50 cps, in contrast to the lesser shift of the C-6 and 1-CH_3 signals (25 and 9–10 cps, respectively), suggests that protonation probably took place on the basic nitrogen, N-4, even though the expected splitting of the 4-methyl signal was not observed. The failure to record a split signal may be caused by too rapid exchange.[9]

The results of this study and our previous work enable us to offer a scheme for classifying types of N-methylamines based on the N-methyl signal of these compounds in their spectra in neutral and acidic solvents. (See Scheme I.)

It is not our purpose to claim an all-inclusive method of grouping types of N-substituted methylamines. There are gaps. Amidines, for example, should be studied. In the aromatic series the effect of other groups which decrease the basicity of the already

(8) The N-methyl signal of 1-methyl-2-pyrrolidone is seen at 170 cps: N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, Spectrum 116.

(9) Experiments are to be undertaken among nonacylated N-methylpiperazines in TFA at varying temperatures to learn whether it is possible to slow down the rate of exchange of the proton on the methylated nitrogen so that splitting of the N-methyl signal can be seen. The results will be published at a later date.

weakly basic N-methylarylamines should be investigated. Among polynitro-N-methylanilines it is not known whether a nitro group at the 2- or 6-position is necessary. There may be others which do not fit the projected scheme. Nevertheless, coupled with other physical methods, the procedure could be helpful in the identification of compounds having an N-methyl group as part of the molecule.

The Ionization Constants of Some 4,5-Substituted 2-Methylpyrimidines

SATOSHI MIZUKAMI AND EIZO HIRAI

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

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An extension of the Hammett's equation to pyrimidines is attempted. The basic ionization constants of 4,5-substituted 2-methylpyrimidines are determined potentiometrically or spectrophotometrically. The base strengths are proportional to σ_m (for 5-substituent) and σ_p (for 4-substituent) values. A method is developed for the use of the Hammett's equation in the elucidation of the amino–imino tautomerism and the protonation equilibrium of 4-aminopyrimidines.

Hammett's equation[1] has played an important part in the investigation of the equilibrium and the mechanism of the reactions for benzene derivatives. Jaffé[2] and Imoto, *et al.*[3] found that this equation could be extended to heterocyclic compounds, such as pyridines, thiophenes, and furans, which have an aromatic structure of six π electrons, without modification. The application of this equation to pyrimidines, however, has never been examined. The authors have carried out the present study in order to extend this equation to the base strength of pyrimidines. Although the basic ionization constants of a number of pyrimidines have been reported,[4,5] there is little data for pyrimidines having a substituent attached to the 5-position in the nucleus. For this purpose we have measured the basic ionization constants of a series of 5-substituted 2-methylpyrimidines having an amino, a dimethylamino, or an alkoxyl group at the 4-position.

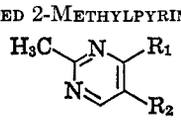
The 4-aminopyrimidines may exist as a corresponding 4-iminodihydropyrimidine resulting from the amino–imino tautomerism.[6] Brown and co-workers[7] have already presented spectroscopic evidence that 4-aminopyrimidine exists largely as the amino form in water. However, little attention has been paid to the effect of substituents on the tautomerism. We shall first examine if their conclusion is universally applicable to 5-substituted 4-amino-2-methylpyrimidines.

Results and Discussion

The basic ionization constants of the pyrimidines studied were determined by potentiometric and spectrophotometric methods, and the thermodynamic corrections[5] were made. The corrected pK_a values are reported in Table I. Plots of the values for the 4-amino- and 4-dimethylamino-2-methylpyrimidines *vs.* the *meta*-substituent constants (σ_m values) are given in Figure 1. The σ_m values are used as a measure of the polar effect of the substituents at the 5-position of the pyrimidines. Figure 1 reveals that for each series of the 4-aminopyrimidines and the 4-dimethylaminopyrimidines, a linear correlation exists between pK_a and σ_m without modification. Table II lists the reaction constants (ρ values) and the intercepts of the lines in Figure 1.

TABLE I

THE BASIC IONIZATION CONSTANTS OF 4,5-SUBSTITUTED 2-METHYLPYRIMIDINES AT 25°



No.	R_1	R_2	pK_a (method)[a]	σ_p[b] (for R_1)	σ_m[b] (for R_2)	$\Sigma\sigma$
1	NH_2	H	6.53 (P)	−0.66	0.00	−0.66
2	NH_2	$CONH_2$	4.97 (P)	−0.66	0.28[c]	−0.38
3	NH_2	COOH	2.14 (S)	−0.66	0.37	−0.29
4	NH_2	$COOC_2H_5$	4.53 (P)	−0.66	0.37	−0.29
5	NH_2	CHO	4.46 (P)	−0.66	0.381[d]	−0.28
6	NH_2	CN	3.51 (S)	−0.66	0.56	−0.10
7	$N(CH_3)_2$	H	7.49 (P)	−0.83	0.00	−0.83
8	$N(CH_3)_2$	$CONH_2$	5.93 (P)	−0.83	0.28[c]	−0.55
9	$N(CH_3)_2$	COOH	1.90 (S)	−0.83	0.37	−0.46
10	$N(CH_3)_2$	$COOC_2H_5$	5.54 (P)	−0.83	0.37	−0.46
11	$N(CH_3)_2$	CN	4.37 (P)	−0.83	0.56	−0.27
12	$NHCOCH_3$	$COOC_2H_5$	1.43 (S)	0.00	0.37	0.37
13	OC_2H_5	$COOC_2H_5$	2.70 (S)	−0.24	0.37	0.13
14	OCH_3	H	3.98 (S)	−0.268	0.00	−0.268
15	OCH_3	OCH_3	4.11 (P, S)	−0.268	0.115	−0.153
16	$OCH(CH_3)_2$	H	4.46 (P)	−0.286[c]	0.00	−0.268
17	OC_6H_5	H	3.17 (S)	−0.028[c]	0.00	−0.028

[a] P, potentiometric method; S, spectrophotometric method. [b] Most of the σ values were those given by D. H. McDaniel and H. C. Brown [*J. Org. Chem.*, **23**, 420 (1958)]. [c] σ values were given by H. H. Jaffé.[9] [d] Reference 1.

For a series of 4-aminopyrimidines, if the amino–imino tautomerism is present, the protonation equilibria may be drawn as shown in Scheme I; that is, IIIa–VIIb may be assumed for the protonated cationic structure. For a series of 4-dimethylaminopyrimidines which necessarily possess the amino structure, only A and B in Scheme I need be considered for the protonation equilibria. The success of the Hammett

(1) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 184.

(2) H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955).

(3) (a) E. Imoto, Y. Ohtsuji, T. Hirai, H. Inoue, R. Motoyama, and H. Kakiuchi, *Nippon Kagaku Zasshi*, **77**, 804 (1956); (b) R. Motoyama, J. Ogawa, and E. Imoto, *ibid.*, **78**, 962 (1957); (c) Y. Ohtsuji, T. Kimura, Y. Sugimoto, E. Imoto, H. Omori, and T. Ohgawara, *ibid.*, **80**, 1021 (1959); (d) Y. Ohtsuji, Y. Koda, E. Imoto, K. Kubo, and M. Furukawa, *ibid.*, **81**, 1293 (1959).

(4) D. J. Brown, "Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, p 464.

(5) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N., Y., 1963, p 1.

(6) G. W. Kenner and A. R. Todd, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 258.

(7) D. J. Brown, H. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1294 (1956).