[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

Some Buffer Solutions with Low Nucleophilic Activity[1]

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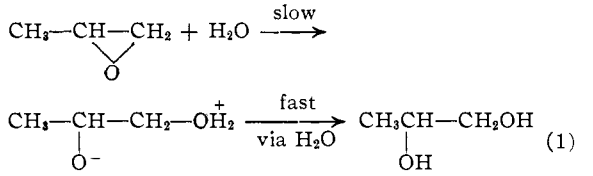
2,6-Dimethylpyridine, 2,4,6-trimethylpyridine, 2-methylquinoline and N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine are shown by kinetic measurements to be unreactive toward propylene oxide in dilute aqueous solution at 50°. These amines may therefore be used, in conjunction with perchloric acid, to form buffer solutions of very low nucleophilic activity for use in the study of reactions sensitive to nucleophilic reagents. In contrast, *cis*-2,6-dimethylpiperidine is found to react readily with propylene oxide and isobutylene oxide. The structure and nucleophilicity of these amines are discussed and details of the preparation and properties of the amine perchlorates are recorded.

Introduction

In the course of recent investigations on the path of the uncatalyzed hydrolysis of epoxides,[2,3] it was found desirable to control the hydrogen ion concentration of the reaction solutions at values in the range of *p*H 6 to 12. However, for many epoxides, hydrolysis in distilled water is accompanied by a fast drift of the *p*H toward the acid region. Since the reactive epoxides combine readily with nucleophilic reagents of all types[4-8] including the anions of common buffer solution components,[9] the introduction of these into the reaction solution gives rise to both rate and product complications. It was found necessary, therefore, to design buffer solutions which would have a negligible nucleophilic activity. We have examined qualitatively, by a simple dilatometric method, the nucleophilic activity of various hindered amines[10] toward propylene oxide in buffered aqueous solutions, in a manner similar to that used by Eastham and co-workers[5] in their studies with ethylene oxide and various nucleophilic amines. Perchloric acid was used in conjunction with the amines to form the buffer solutions since the low nucleophilic activity of the perchlorate ion is well established.[11]

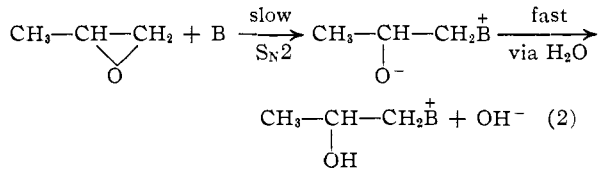
The hydrolysis of propylene oxide in pure water is known to proceed at a constant rate over the *p*H range 6 to 12, most probably by a scheme similar to that shown in equation 1.[3]

As expected from consideration of the higher densities of glycols compared to the corresponding epoxides, reaction 1 is accompanied by a marked diminution in the volume of the reaction mixture which is proportional to the percentage reaction for dilute solutions of reactants. Tertiary amines such as pyridine should also add to epoxides, to



(1)

form quaternary ammonium hydroxides as in equation 2.



(2)

This reaction should also be accompanied by a diminution in the total volume of the reacting solution. Hence, in our experiments, nucleophilic character in the tertiary amine B should be shown by two criteria. Firstly, if the neutral amine is consumed in reaction with excess of propylene oxide, so producing hydroxide ions, the *p*H of the reaction solution should increase throughout the reaction. Secondly, the apparent dilatometric rate of neutral hydrolysis of the propylene oxide should increase with increasing concentration of the free amine in the buffer solution. In contrast, the hydrolysis of propylene oxide in a solution buffered by a truly anucleophilic amine should show ideally a constant rate for all concentrations of buffer and a constant *p*H throughout the reaction.

In this paper, we report the results of these rate studies together with details of the preparation and properties of the perchlorates of some amines of low nucleophilic activity toward propylene oxide. It is suggested that these and similar compounds may find application as buffer solution components in other fields of research.

Experimental

The Buffer Solutions.—Recrystallization of their salts offered the best means of purifying pyridine and its derivatives. Therefore, it was convenient to make up the buffer solutions from weighed samples of the pure amine perchlorates. These were dissolved, partially neutralized with potassium hydroxide solution and made up to a known volume. The *p*H values of these buffer solutions were recorded, using a standardized Beckman *p*H meter with a glass electrode, at the time of preparation and again at room temperature at the conclusion of the kinetic run with propylene oxide (after *ca.* 36 hours).

Values for the basic ionization constants (K_B) for the amines under study were calculated from the observed *p*H

(1) Work supported by a grant from the Atomic Energy Commission.

(2) J. G. Pritchard and F. A. Long, THIS JOURNAL, **78**, 6008 (1956).

(3) F. A. Long and J. G. Pritchard, *ibid.*, **78**, 2663 (1956).

(4) *Halide ions, thiosulfate ion.* J. N. Bronsted, M. Kilpatrick and M. Kilpatrick, *ibid.*, **51**, 428 (1929).

(5) *Pyridine, aliphatic amines.* M. Eastham, B. de B. Darwent and P. W. Beaubien, *Can. J. Chem.*, **29**, 575, 585 (1951).

(6) *Azide ion.* C. A. VanderWerf, R. Y. Heisler and W. E. McEwen, THIS JOURNAL, **76**, 1231 (1954).

(7) *Nitrate ion.* W. L. Petty and P. L. Nichols, Jr., *ibid.*, **76**, 4385 (1954).

(8) *Thiocyanate ion.* P. L. Nichols, Jr., and J. D. Ingham, *ibid.*, **77**, 6547 (1955).

(9) *Acetate and benzoate ions.* W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(10) We were prompted to tests derivatives of pyridine in which the nitrogen atom is hindered by substituents in the 2,6-positions by some work of S. Seltzer and F. H. Westheimer (private communication) in which 2,6-dimethylpyridine was used successfully to form a non-chelating buffer solution for the study of the metal ion promoted decarboxylation of dimethyloxaloacetic acid.

(11) *Cf.* K. A. Hoffmann, G. A. Zedwitz and H. Wagner, *Ber.*, **42**, 4390 (1909).

values of aqueous solutions containing the amine perchlorates (0.0050 *M*) and exactly one-half of an equivalent of potassium hydroxide (0.0025 *M*) in each case. The definitions of K_B and pK_B are shown from the equations

$$B + H_2O \rightleftharpoons BH^+ + OH^- \quad (3)$$

$$K_B = C_{BH^+}C_{OH^-}/C_B, \qquad pK_B = -\log_{10} K_B \quad (4)$$

$$pK_B = 14.0 - pH + \log_{10} C_B/C_{BH^+} \quad (5)$$

For the first four bases in Table I, the equilibrium concentration of OH^- is so small compared to C_B and C_{BH^+} that C_B remains essentially equal to C_{BH^+} and the last term on the right-hand side of equation 5 is zero. For the derivatives of piperidine, which buffer in the *p*H range 10.5–11.0, the value of C_B/C_{BH^+} was calculated from equation 3 and included in the calculation of pK_B by equation 5. Table I records the results of our measurements (at 22 ± 2°) together with some literature values of pK_B where available. The agreement between these is quite satisfactory.

TABLE I

pK_B VALUES AT 20 TO 25° FOR THE IONIZATION OF NEUTRAL AMINE BASES IN WATER

Amine	*p*H 50/50	pK_B from 50/50 buffer	pK_B Lit. values
Pyridine	5.20	8.80	8.85[12]; 8.77[13]
2-Methylquinoline	5.74	8.26	8.6[14]; 8.2[15]
2,6-Dimethylpyridine	6.72	7.28	7.41[12]; 7.38[13]
2,4,6-Trimethylpyridine	7.46	6.54	6.55[13]
N-(2-Hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine	10.53	3.35	.....
cis-2,6-Dimethylpiperidine	10.86	2.69	.....

Rate Comparisons.—Standard dilatometric technique was used[2,16] with dilatometers of *ca.* 8-ml. capacity. All buffer solutions were thoroughly degassed before addition of propylene oxide The complete hydrolysis of 8 ml. of 0.3 molar propylene oxide gave a meniscus displacement of *ca.* 15 cm. in capillaries of 0.05 cm. internal diameter. The rate equation for the hydrolysis reaction of equation 1 is $-dC_{oxide}/dt = k_1 C_{oxide}$. First-order rate coefficients in sec.$^{-1}$ units were calculated by the Guggenheim method. For those runs with pyridine and 2,6-dimethylpiperidine which involved an abnormally large volume change in the dilatometer due to the nucleophilic activity of these compounds, relative initial rates were calculated by extrapolating the volume diminution data back to the time of mixing the reactants at 50°. Except for these abnormal runs, all rate data gave good straight-line Guggenheim plots. The temperature of the water-bath was controlled at 50 ± 0.01°.

Materials.—Reagent grade inorganic chemicals were used throughout. Reagent grade propylene oxide was distilled before use: b.p. 35°, $n^{25}D$ 1.3638. The perchlorates of the amine bases were prepared and purified as described below, giving good yields except where stated.

Pyridine perchlorate was purified by crystallization from ethyl alcohol giving white crystals of m.p. 289–290°.[17] A solution of 10.5 ml. of 60% perchloric acid and 12 ml. of technical (90%) 2,6-lutidine in 100 ml. of ethyl alcohol was evaporated at 100° and allowed to crystallize. Recrystallization of the product from acetone gave white, crystalline **2,6-dimethylpyridinium perchlorate**, m.p. 110–111°; found C = 40.4%, H = 4.8%, N = 6.7%, as required by $C_7H_{10}O_4NCl$. 11.5 ml. of reagent grade 2,4,6-trimethylpyridine treated as above gave white, crystalline **2,4,6-trimethylpyridinium perchlorate**, m.p. 239–240°; found C = 43.5%, H = 5.4%, N = 6.2%, as required for $C_8H_{12}O_4NCl$ (N = 6.3%). (This substance assumed a faint orange color on exposure to light.) Evaporation of a solution containing 11 ml. of reagent grade quinaldine and 10.5 ml. of 60% perchloric acid in 50 ml. of ethyl alcohol gave a red wine-colored crystalline mass. Repeated recrystallization from alcohol gave straw-colored crystals of **2-methylquinolinium perchlorate**, m.p. 129–130°; found C = 49.1%, H = 4.1%, N = 5.5% ($C_{10}H_{10}O_4NCl$ requires C = 49.2%, H = 4.3%, N = 5.7%).

A solution containing 10 ml. of (*cis*)-2,6-dimethylpiperidine[18] and 9.5 ml. of 60% perchloric acid in 25 ml. of ethyl alcohol was evaporated at 100° and allowed to crystallize. The product was recrystallized from 1,4-dioxane giving fine, white needles of ***cis*-2,6-dimethylpiperidinium perchlorate**, m.p. 186–187°; found C = 39.5%, H = 7.7%, N = 6.4% ($C_7H_{16}O_4NCl$ requires C = 39.4%, H = 7.5%, N = 6.5%).

A solution containing 15 ml. of *cis*-2,6-dimethylpiperidine and 11 ml. of isobutylene oxide in 200 ml. of water was allowed to stand overnight at room temperature. The oily layer which had formed above the aqueous phase was separated and neutralized with alcoholic 20% perchloric acid solution. Evaporation of the alcohol and water present gave a crystalline mass of which only a small part was soluble in ethyl acetate. After washing with boiling ethyl acetate, to remove unreacted 2,6-dimethylpiperidine, the product was recrystallized from a solvent containing equal volumes of ethyl alcohol and ethyl acetate, and gave 2 g. of **N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidinium perchlorate**, m.p. 200°; found C = 46.4%, H = 8.4%, N = 4.85%. ($C_{11}H_{24}O_5NCl$ requires C = 46.2%, H = 8.4%, N = 4.9%.)[19] It should be noted that the formation of N-(1,1-dimethyl-2-hydroxyethyl)-*cis*-2,6-dimethylpiperidine in this last reaction may be excluded immediately on steric grounds since the nucleophilic reaction of even the small hydroxide ion with isobutylene oxide occurs almost exclusively at the primary carbon atom of the epoxide ring.[3]

Results

Table II gives the observed first-order rate coefficients for reaction of 0.3 molar propylene oxide at 50° in a series of buffer solutions having two general ranges of concentration. The initial concentrations of free amine in the solutions were calculated using the pK_B values of Table I and the observed initial *p*H values of the reaction solutions.

Since pyridine is known to react readily with propylene oxide[20,21] the results of expts. 1 and 7 exemplify the behavior of a typical nucleophile. In both experiments there is observed a large drift of the *p*H during the reaction, and the rate of volume diminution in the dilatometer is increased about sevenfold on increasing the initial free pyridine concentration from 0.002 to 0.08 molar. A similar behavior is shown by *cis*-2,6-dimethylpiperidine in expts. 2 and 8, and we therefore conclude that this compound exerts a nucleophilic activity similar to that of pyridine.

Completely contrasting behavior is observed for the hindered amines of expts. 4, 5 and 6. For these cases, the *p*H is constant throughout each reaction and the three values of k_1 are identical and somewhat lower than those obtained in expts. 1 and 2. The results of expts. 10, 11 and 12 show that for in-

(12) E. F. G. Herington, *Faraday Soc. Disc.*, **9**, 26 (1950).

(13) A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951).

(14) W. A. Felsing and B. S. Biggs, THIS JOURNAL, **55**, 3624 (1933).

(15) C. Golumbic and M. Orchin, *ibid.*, **72**, 4145 (1950).

(16) J. G. Pritchard and F. A. Long, *ibid.*, **78**, 2667 (1956).

(17) F. Arndt and P. Nachtwey, *Ber.*, **59B**, 446, 448 (1926), give m.p. 288°.

(18) We are indebted to the Reilly Tar and Chemical Corporation for a sample of 2,6-dimethylpiperidine which had b.p. 128°, $n^{25}D$ 1.4370 and which gave a unique hydrochloride of m.p. 278–279° (first crystallization). The sample therefore almost certainly had the *cis* configuration since it was identical with 2,6-dimethylpiperidine prepared by the catalytic reduction of 2,6-dimethylpyridine by hydrogen over nickel. *Cf.* A. Marcuse and R. Wolffenstein, *Ber.*, **32**, 2528 (1899); H. Adkins, L. F. Kuick, M. Farlow and B. Wojcik, THIS JOURNAL, **56**, 2427 (1934).

(19) Microanalyses were by the Schwarzkopf Microanalytical Laboratory, 56-19—37th Avenue, Woodside 77, N. Y.

(20) J. Hansson, *Svensk Kem. Tid.*, **60**, 183 (1948).

(21) L. Smith, S. Mattsson and S. Andersson, *C. A.*, **41**, 6458i (1947).

TABLE II

DILATOMETRIC RATE COEFFICIENTS FOR WATER REACTION OF 0.3 MOLAR PROPYLENE OXIDE IN A SERIES OF AMINE BUFFER SOLUTIONS AT 50°

Expt.	Amine	Buffer ratio C_B/C_{BH^+}	Approx. free amine concn. (C_B)	pH initial	pH final	10^3k_1 (sec.$^{-1}$)
1	Pyridine	2/3[a]	0.002[a]	5.0	11.0	10.4
2	*cis*-2,6-Dimethylpiperidine	2/3[a]	.002[a]	11.0	10.2	10.6
3	2-Methylquinoline	1	.0025	5.7	5.7	10.7
4	2,6-Dimethylpyridine	2/3	.002	6.4	6.5	8.6
5	2,4,6-Trimethylpyridine	2/3	.002	7.3	7.3	8.6
6	N-(2-Hydroxy 2-methylpropyl)-*cis*-2,6-dimethylpiperidine	3/7	.0015	10.3	10.2	8.5
7	Pyridine	2/3[a]	.08[a]	5.0	12.0	65[b]
8	*cis*-2,6-Dimethylpiperidine	2/3[a]	.08[a]	11.0	10.4	58[b]
9	2-Methylquinoline	1	.025	5.7	5.7	12.1
10	2,6-Dimethylpyridine	1	.10	6.7	6.7	9.3
11	2,4,6-Trimethylpyridine	2/3	.08	7.3	7.3	8.8
12	N-(2-Hydroxy 2-methylpropyl)-*cis*-2,6-dimethylpiperidine	4/5	.016	10.6	10.5	8.4

[a] Initially. [b] Comparative initial rates.

creased concentrations of the same hindered amines, the pH values of the reaction solutions still remain constant and the k_1 values are essentially the same as those obtained in expts. 4, 5 and 6. The small variations in k_1 for these last three expts. of Table II were not outside the *possible* experimental error (± *ca.* 10%) but may actually have been due to small kinetic salt effects. In expts. 9 and 12, the maximum buffer concentrations were limited for solubility reasons. Nevertheless, the free amine concentration of about 0.02 molar was considered adequate to detect dilatometrically any nucleophilic activity. (A comparison of the expts. 1 and 2 with expts. 4, 5 and 6 shows that a concentration of as little as 0.002 molar of a strongly nucleophilic amine gives rise to a detectable increase in the observed value of k_1.) We conclude that the true rate of the uncatalyzed hydrolysis of propylene oxide at 50° is 8.6×10^{-6} sec.$^{-1}$. The good reproducibility of the dilatometric rates leads us to believe that this figure is correct to within ±3%. We conclude also that the hindered amines 2,6-dimethyl- and 2,4,6-trimethylpyridine and N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine have a low nucleophilic activity with respect to propylene oxide.

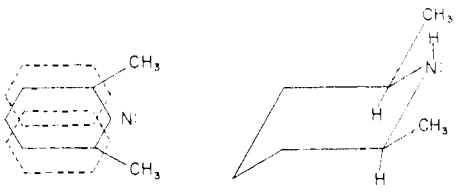
The case of 2-methylquinoline might appear to be anomalous since it gives k_1 values which are consistently high while the pH during the reaction remains constant at a value of 5.7. The high k_1 values are almost certainly due to the incursion of a small contribution from the acid-catalyzed mode of hydrolysis which would be expected to enter with propylene oxide at pH values below *ca.* 6.0.[3,4] However, the constancy of the pH in both expts. 3 and 9 gives very strong evidence for the very low nucleophilic activity of 2-methylquinoline. In expt. 1 with pyridine, a larger k_1 value might possibly have been expected for the same reason since the reaction was started at pH 5, in the acid-catalyzed region. However, it is highly probable that the pH of the solution drifted into the "neutral" region (pH 6 to 12) during the first few minutes of the reaction, before the first reading of the dilatometer.

Reaction of the Nucleophilic Amines.—The increase of pH for the reaction of propylene oxide with the pyridine buffer solutions in expts. 1 and 7 is the expected result from the formation of an aromatic quaternary ammonium hydroxide.[5] Initially, for such a reaction, the pH drift should be small since the hydroxide ion produced would be almost wholly neutralized by the pyridinium ion. However, this process increases the C_B/C_{BH^+} ratio, and when about half of the total amine has been used up this ratio becomes very large, causing the pH to drift rapidly into the alkaline region. Experiments designed to isolate a product from this reaction gave results in agreement with previous work on similar systems. Namely, the N-(2-hydroxypropyl)-pyridinium hydroxide cannot be isolated as it polymerizes, especially in contact with air, to a dark bro n viscous substance[22]; and whereas the N-(2-hydroxypropyl)-pyridinium halides are reported to be crystallizable,[23,24] the perchlorate salt was found to remain as a viscous oil.[25] The matter was not pursued beyond these qualitative observations.

The pH drift accompanying the nucleophilic reaction of *cis*-2,6-dimethylpiperidine with propylene oxide is directed toward the acid region. Since 2,6-dimethylpiperidine is a secondary amine the product of this reaction by equation 2 should be a tertiary amine and there should be no production of hydroxide ion. Hence, the observed direction of the pH drift in expts. 2 and 8 is consistent with the fact that tertiary amines are generally less basic than the secondary amines from which they are derived. A pertinent example of this is shown by a comparison of the pK_B values in Table I for *cis*-2,6-dimethylpiperidine and its tertiary N-(2-hydroxy-2-methylpropyl) derivative, which was obtained by reaction of isobutylene oxide with the *cis*-2,6-dimethylpiperidine. In this one case, the tertiary amine was prepared in quantity and isolated as its perchlorate since it promised and proved to be a good anucleophilic buffer component for pH *ca.* 10. Experiments are in progress to investigate other members of this class of compounds.

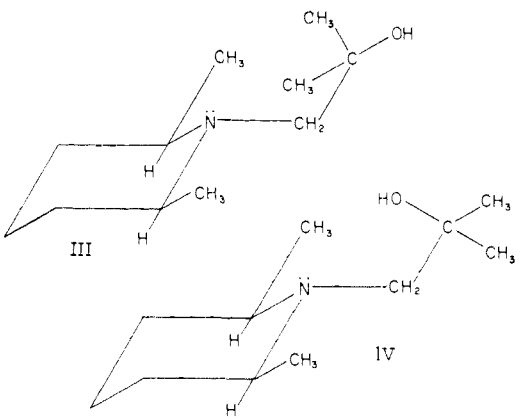
(22) H. Lohmann, *J. prakt. Chem.*, **153**, 57 (1939).
(23) A. M. Eastham, *J. Chem. Soc.*, 1936 (1952).
(24) F. N. Hayes, L. C. King and D. E. Peterson, THIS JOURNAL, **78**, 2527 (1956).
(25) L. C. King, N. Beret and F. W. Hayes, *ibid.*, **71**, 3498 (1949).

Structural Considerations.—The observed sharp drop in reactivity with propylene oxide on going from pyridine to 2,6-dimethylpyridine (I) is entirely consistent with many other studies of steric effects[26–28] and suggests that the steric requirements for reaction of I with epoxides are quite specific. In an S_N2 reaction involving opening of the epoxide ring in the *trans* sense,[29] the nitrogen atom in I is probably so well shielded by the methyl substituents and the two branches of the π-electron shell of the pyridine ring that this reaction is very slow. The same applies to 2,4,6-trimethylpyridine and to 2-methylquinoline.



I II

2,6-Dimethylpyridine *cis*-2,6-Dimethylpiperidine
(Dotted line indicates π-shell)



III IV

N-(2-Hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine

The observed high reactivity of *cis*-2,6-dimethylpiperidine (represented by II for one of the four possible configurations) is interesting since from an examination of scale models there appears to be no obvious structural reason why the nucleophilic activities of I and II should be so different toward propylene oxide. However, in I the unshared electrons of the nitrogen atom lie in a plane trigonal sp^2 hybrid orbital directed along the axis of symmetry of I, but in II they lie in a tetrahedral sp^3 orbital which may be directed with respect to the piperidine ring either equatorially as shown in II or axially, depending on inversion of the configuration about the nitrogen atom. Also, owing to their greater "p" character, sp^3 orbitals extend out further from the atomic nucleus than do sp^2 orbitals. The nucleophilic electrons on II should thus be more available than those in I, leading to the much higher basicity and nucleophilic activity of II.[30] From a consideration of models, we consider that the S_N2 reaction of isobutylene oxide with *cis*-2,6-dimethylpiperidine would be most likely to occur through configuration II. Hence, the product from *trans* addition to the epoxide ring would at first be expected to have the structure III. However, the stable modification of this molecule may be the less congested and possibly weakly hydrogen bonded structure IV, since C–C bond rotations in both structures are restricted. The formation of a tertiary ammonium ion by reaction of III or IV with a molecule as large as propylene oxide appears almost impossible on steric grounds, so that the demonstration in this paper of the low or undetectably nucleophilic activity of N-(2-hydroxy-2-methylpropyl)-*cis*-2,6-dimethylpiperidine is easily understood.

As H. C. Brown and co-workers point out,[26] the actual magnitude of a steric effect is dependent on the particular steric requirements of the reaction considered. However, since the epoxide ring is generally considered to be very sensitive to nucleophiles, it is probable that the low nucleophilic activity of the hindered amines discussed in this paper is general toward most types of organic substrate containing two or more carbon atoms.

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(26) H. C. Brown, D. Gintis and L. Domash, THIS JOURNAL, **78**, 5387 (1956). This article deals particularly with substituted pyridine derivatives and gives references to other studies by Brown and co-workers: see especially H. C. Brown and G. K. Barbaras, *ibid.*, **69**, 1137 (1947).

(27) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409 (1953).

(28) J. W. Baker and W. S. Nathan, *ibid.*, 519 (1935.)

(29) S. Winstein and R. B. Henderson, in Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, New York, N. Y., 1950, p. 29.

(30) *Cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 174.