

# Stability of Pyridine-2-aldoxime Methiodide II

## Kinetics of Deterioration in Dilute Aqueous Solutions

By ROBERT I. ELLIN, JAMES S. CARLESE, and ALBERT A. KONDRITZER

The decomposition of 2-PAM was studied at pH values 0.5 to 13 and at temperatures ranging from 37 to 87°. At constant pH and temperature, the observed rate of deterioration of 2-PAM was first order with respect to drug concentration. Below pH approximately 4, hydrogen ion catalysis of the acid form of oxime occurs; above pH 4, the reaction is either an hydroxyl ion catalysis of the acid form of oxime or is noncatalytic in which there is a direct attack on the oximate species. Two mechanisms have been postulated for the breakdown of 2-PAM. Specific velocity constants, energies of activation, and frequency factors have been determined for both mechanisms. The pH of maximum stability has been determined from initial rate constants over the entire pH range. General equations relating the half-life of 2-PAM solutions to temperature and pH have been derived.

DURING the past few years a group of new drugs, of which the best known is pyridine-2-aldoxime methiodide (2-PAM, 2-formyl-1-methylpyridinium iodide oxime), has been introduced which is capable of reversing neuromuscular block caused by organophosphates and may be of clinical value in the treatment of intoxication by these compounds (1-6). Aqueous solutions of 2-PAM, contained in injector items, may be used for purposes of self-aid and first-aid. Therefore, knowledge of the stability in water is essential. The object of this study was to establish a basis for predicting the rate of decomposition of 2-PAM at various hydrogen and hydroxyl ion concentrations and temperatures.

The hydrolysis and pyrolysis of acylated oximes have been the subject of many investigations (7-9). The hydrolysis of free oximes in acid solution has been well investigated (10). However, relatively few references are available on the alkaline decomposition of the free oxime. For the most part, these reports were not concerned with the kinetics of the process or predictions based on such data. Bengner and Brady (11) presented various mechanisms for the alkaline hydrolysis of acyl benzaldoximes. Two of the mechanisms described were attack by hydroxyl ions: (a) at the methine hydrogen atom resulting in formation of the corresponding nitrile and (b) at the carbonyl carbon resulting in the formation of free oxime. In general, aldoximes on reaction with alkali do not give rise to the corresponding nitrile because the high electron density on the oxygen prevents attack by hydroxyl ions at the methine hydrogen atom. Replacement of the hydrogen of the hydroxyl group of the

oxime by an acyl group establishes a relative positive charge at the oximino oxygen, thereby reducing the electron density sufficiently to permit hydroxyl ion attack at the methine hydrogen atom (11, 12). This mechanism is considered to involve removal of the methine hydrogen atom as a proton accompanied or followed by release of the acylate anion (11, 13). On the other hand, the free aldoxime, *o*-nitrobenzaloxime, on heating with aqueous sodium hydroxide gives rise to the corresponding nitrile. Here the negative inductive effect of the nitro group facilitates the removal of a proton at the methine hydrogen atom (14, 15).

The decomposition of 2-PAM takes place by two mechanisms. Below pH approximately 4, 2-PAM is hydrolyzed to pyridine-2-carboxaldehyde methiodide and hydroxylamine (reaction 2, Fig. 1). Above pH 4, 2-PAM is dehydrated to 2-cyanopyridine methiodide, which is converted to 2-hydroxypyridine methiodide, which rearranges to *N*-methyl- $\alpha$ -pyridone (16) (reaction 1, Fig. 1). The latter reaction may follow a mechanism similar to the one mentioned above. The nitrogen on the pyridine ring, being strongly electrophilic, would have an effect similar to that of a nitro group and thereby facilitate hydroxyl ion attack on the methine hydrogen atom.

The kinetics of the decomposition of 2-PAM was studied over the pH range 0.5 to 13 and at the temperatures 37, 57, and 87°. Kinetic constants, determined at the various temperatures, were used to calculate the activation energy for each of the two mechanisms. From these values an equation was derived for predicting the decomposition of 2-PAM at any particular temperature and pH. By taking into account the effects of both hydroxyl and hydrogen ions, the pH of minimum decomposition at various tem-

Received January 14, 1961, from the Physiology Division, Directorate of Medical Research, U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Md.

Accepted for publication March 28, 1961.

Part I was published in *J. Am. Chem. Soc.*, **80**, 6588 (1958).

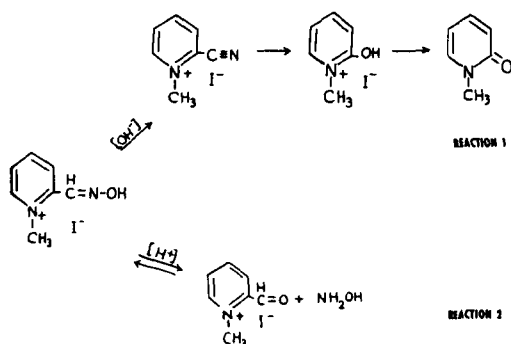


Fig. 1.—Reactions involved in the decomposition of 2-PAM.

peratures and the decomposition rates at these minimum pH values were calculated. By using initial rate constants, the half-life of 2-PAM solutions have been calculated for various pH values and temperatures.

### EXPERIMENTAL

The method of analysis consisted of making a series of ultraviolet measurements of 2-PAM solutions undergoing decomposition. (2-PAM, purchased from Aldrich Chemical Co., Milwaukee, Wis., was twice recrystallized from ethyl alcohol and has a melting point of 228–230°.) Ultraviolet absorption spectra of 2-PAM and its acid and base decomposition products were determined in acid and alkaline solutions and indicated that 2-PAM can be determined quantitatively in the presence of its decomposition products at 335  $m\mu$  in 0.1 *N* sodium hydroxide (17).

The hydrogen and hydroxyl ion concentrations of the system were maintained by using buffer solutions or an excess of acid and base. The pH change during the experimental period was limited to 0.1 pH unit. Buffer systems used in the study are listed in Table I. From pH 0.4 to 1.2, the pH was controlled by an excess of perchloric acid; at pH 13, by an excess of sodium hydroxide. The pH of each

TABLE I.—LIST OF BUFFERS EMPLOYED AND COMPOSITION OF EACH

pH	Composition	Dilution
2	5.0 ml. 0.2 <i>M</i> KCl + 10.6 ml. 0.2 <i>N</i> HCl	to 200 ml.
3	3 Gm. glacial acetic acid	to 500 ml.
4	16 ml. 0.1 <i>N</i> acetic acid + 4 ml. of 0.1 <i>N</i> sodium acetate	as is
5	6 ml. of 0.1 <i>N</i> acetic acid + 14 ml. of 0.1 <i>M</i> sodium acetate	as is
6	11.6 Gm. $\text{KH}_2\text{PO}_4$ + 2.15 Gm. $\text{Na}_2\text{HPO}_4$	to 500 ml.
7	4.55 Gm. $\text{KH}_2\text{PO}_4$ + 9.45 Gm. $\text{Na}_2\text{HPO}_4$	to 500 ml.
8	5.9 Gm. boric acid + 4.55 Gm. borax	to 500 ml.
10	3.25 Gm. $\text{NaHCO}_3$ + 6.6 Gm. $\text{Na}_2\text{CO}_3$	to 500 ml.
12	12.3 Gm. $\text{Na}_3\text{PO}_4$	to 500 ml.

buffer was determined at the temperatures at which the experiments were carried out.

Buffer solutions were placed in a thermostatically controlled bath, and allowed to reach the temperature of the bath. A volume of standard solution, containing 25 mg./ml. of 2-PAM, was then added to give the reaction mixture a concentration of 1 mg./ml. The decomposition of 2-PAM was determined by periodically removing 1-ml. samples, diluting to 100 ml. with 0.1 *N* sodium hydroxide, and following the disappearance of the oxime grouping with a Beckman DU quartz spectrophotometer at 335  $m\mu$ .

### RESULTS AND DISCUSSION

The observed degradation of 2-PAM under various conditions, examples of which are given in Figs. 2–4, conform to the classical first-order equation,  $\ln c = kt + \text{constant}$ , where  $k$  is the first-order rate constant at a constant pH. 2-PAM as the free oxime represents the protonated form of the oxime and will be designated (OxH). The protonated form is positively charged as the nitrogen of the pyridine ring of 2-PAM is in the charged form. The basic or oximate species of 2-PAM may be considered to be electrically neutral as the negative charge on the oximino oxygen internally neutralizes the positive charge on the pyridine ring nitrogen. The oximate species will be designated (Ox).

From the pH profile shown in Fig. 5 we can assume that the hydrolysis of 2-PAM at pH values 0–4 is due to the hydrogen ion catalysis of the protonated species. At pH values 4 to 8, the mech-

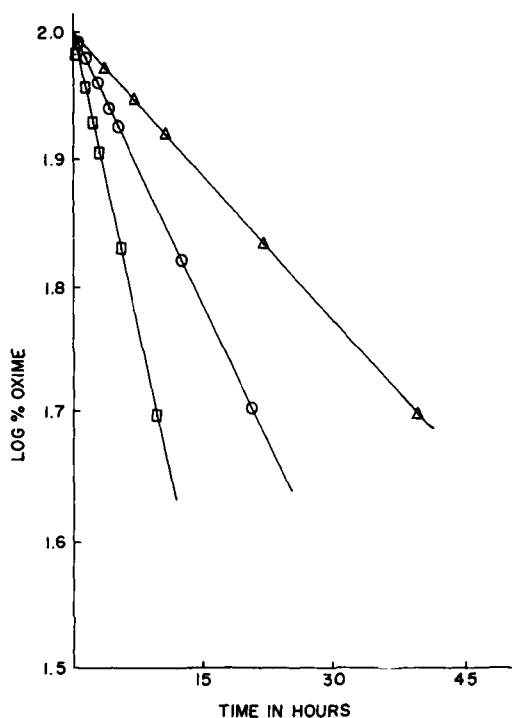


Fig. 2.—Typical first-order rate plots for the acid catalyzed decomposition of 2-PAM at 57°.  $\Delta$ , 0.096 *N*;  $\circ$ , 0.191 *N*;  $\square$ , 0.383 *N* perchloric acid.

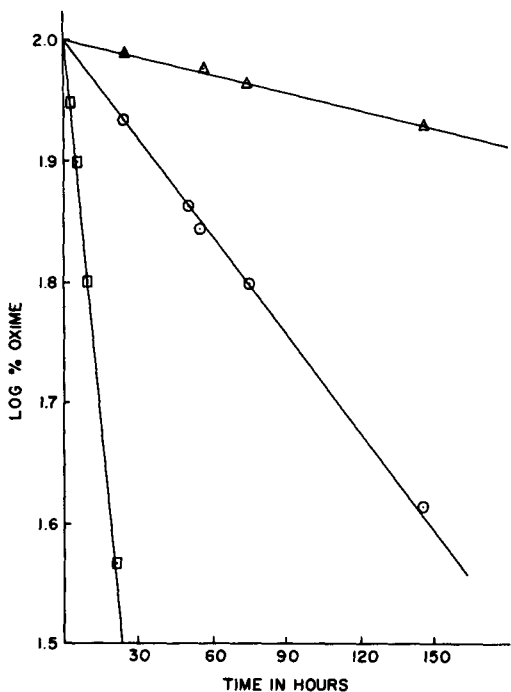


Fig. 3.—Typical first-order rate plots for the decomposition of 2-PAM at pH values 5 to 7 at 57°.  $\Delta$ , pH 5;  $\circ$ , pH 6;  $\square$ , pH 7.

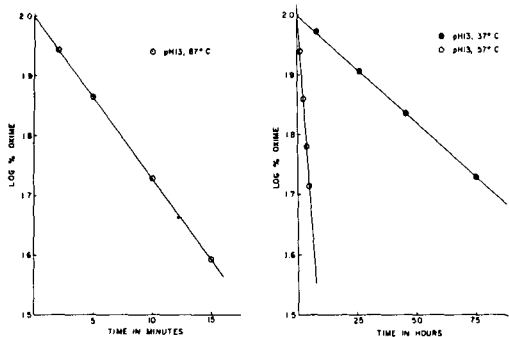


Fig. 4.—Typical first-order rate plots for the decomposition of 2-PAM at pH 13 at various temperatures.

anism appears to involve hydroxyl ion catalysis of the oxime species of 2-PAM. However, a pH independent region is observed at the pH values approximately 8–13. Thus at pH values 4 to 13, equations can be derived to show the mechanism of degradation involves either hydroxyl ion catalysis of the oxime species or a direct attack on the oximate species of 2-PAM, in which there is no catalysis.

The symbol  $k_{H^+}$  represents the catalytic rate constant or catalytic coefficient for the hydrogen ion catalysis of the protonated species,  $k_{OH^-}$  represents the catalytic constant for the hydroxyl ion catalysis of the protonated species,  $k_{Ox}$  represents the degradation constant acting directly on the oximate species of 2-PAM,  $a$  is the total drug concentration, and  $Ka$

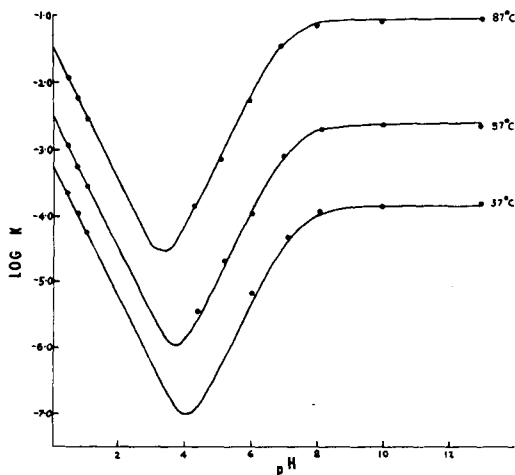


Fig. 5.—The pH profile of the logarithm of initial first-order rate constants for the breakdown of 2-PAM at 37, 57, and 87°. The curves represent values calculated from the equation derived from experimental data. The illustrated points represent experimental values.

and  $Kw$  are the acid and water dissociation constants, respectively. Then

$$\frac{d \ln a}{dt} = k_{H^+} (H^+) \frac{(H^+)}{Ka + (H^+)} + \frac{k_{OH^-} kw}{Ka + (H^+)} \quad (\text{Eq. 1})$$

or

$$\frac{d \ln a}{dt} = k_{H^+} (H^+) \frac{(H^+)}{Ka + (H^+)} + \frac{k_{Ox} Ka}{Ka + (H^+)} \quad (\text{Eq. 2})$$

The right sides of Eqs. 1 and 2 are constant at any given pH. The overall rate of degradation is first order with respect to oxime concentration and  $(d \ln a/dt)pH = k$ , the overall pseudo first-order rate constant at a constant pH.

Whenever the first term of Eqs. 1 and 2 is important, that is, the value of the hydrogen ion concentration is much larger than the value of  $Ka$ , the oxime exists in the protonated form. Therefore, at any pH the equations reduce, respectively, to

$$k = k_{H^+} (H^+) + \frac{k_{OH^-} kw}{Ka + (H^+)} \quad (\text{Eq. 3})$$

and

$$k = k_{H^+} (H^+) + \frac{k_{Ox} Ka}{Ka + (H^+)} \quad (\text{Eq. 4})$$

Hence,  $k_{OH^-}$  will be related to  $k_{Ox}$  at any given pH and temperature by the statement

$$k_{Ox} = k_{OH^-} Kb \quad (\text{Eq. 5})$$

where  $Kb$  is the basic dissociation constant of 2-PAM.

At relatively high pH values, approximately 10 to 14, Eq. 3 reduces to  $k = k_{OH^-} - Kb$  and Eq. 4 reduces to  $k = k_{Ox}$ . At relatively low pH values below 3, Eqs. 3 and 4 reduce to  $k = (k_{OH^-} - Kw)/Ka + (H^+)$  and Eq. 4 reduces to  $k = k_{Ox}Ka/(Ka + (H^+))$ .

TABLE II.—OBSERVED RATE CONSTANTS ( $k$  in  $\text{min.}^{-1}$ ) FOR THE SPECTROPHOTOMETRICALLY DETERMINED DEGRADATION OF 2-PAM

37°		57°		87°	
pH	$k, \text{min.}^{-1}$	pH	$k, \text{min.}^{-1}$	pH	$k, \text{min.}^{-1}$
13	$1.54 \times 10^{-4}$	13	$2.17 \times 10^{-3}$	13	$8.77 \times 10^{-2}$
9.96	$1.39 \times 10^{-4}$	9.98	$2.15 \times 10^{-3}$	9.81	$7.81 \times 10^{-2}$
8.05	$1.15 \times 10^{-4}$	8.14	$2.01 \times 10^{-3}$	8.01	$6.62 \times 10^{-2}$
7.10	$4.53 \times 10^{-5}$	7.02	$8.03 \times 10^{-4}$	6.91	$3.30 \times 10^{-2}$
5.88	$6.06 \times 10^{-6}$	6.06	$1.04 \times 10^{-4}$	5.95	$5.23 \times 10^{-3}$
		5.21	$1.95 \times 10^{-6}$	5.10	$6.96 \times 10^{-4}$
		4.32	$3.65 \times 10^{-6}$	4.30	$1.36 \times 10^{-4}$
1.02	$5.60 \times 10^{-5}$	1.02	$2.89 \times 10^{-4}$	1.02	$2.75 \times 10^{-3}$
0.72	$1.15 \times 10^{-4}$	0.72	$5.36 \times 10^{-4}$	0.72	$5.62 \times 10^{-3}$
0.42	$2.25 \times 10^{-4}$	0.42	$1.15 \times 10^{-3}$	0.42	$1.15 \times 10^{-2}$

TABLE III.—PREDICTED STABILITY OF 2-PAM AT pH OF MINIMUM HYDROLYSIS

$t, ^\circ\text{C.}$	pH min.	$t^{1/2}, \text{yr.}$
0	4.93	3,000
10	4.68	800
20	4.44	160
25	4.36	80
30	4.23	38
37	4.07	13.5
40	4.02	9.5
50	3.85	2.5
57	3.74	1.15
60	3.69	0.75
70	3.54	0.25
80	3.40	0.1
87	3.32	0.05
100	3.20	5 days

Between the regions of high and low pH the reaction velocity will pass through a minimum at a hydrogen ion concentration which is found by differentiating  $k$  with respect to  $(\text{H}^+)$  in Eqs. 3 or 4, and equating to zero. For Eq. 3

$$k \text{H}^+ - \frac{k_{\text{OH}^-} \text{Kw}}{(\text{K}_a + \text{H}^+)^2} = 0 \quad (\text{Eq. 6})$$

At the observed pH of minimum decomposition, shown to be about pH 4,  $\text{K}_a$  is small compared to  $\text{H}^+$  and can be dropped from the equation. Then

$$(\text{H}^+_{\text{M}})^2 = \frac{k_{\text{OH}^-} \text{Kw}}{k_{\text{H}^+}} \quad (\text{Eq. 7})$$

For Eq. 4

$$(\text{H}^+_{\text{M}})^2 = \frac{k_{\text{Ox}} \text{K}_a}{k_{\text{H}^+}} \quad (\text{Eq. 8})$$

The value  $k_{\text{M}}$ , the velocity constant at  $(\text{H}^+_{\text{M}})$ , is obtained by substituting in Eqs. 3 and 4 the corresponding values of  $k_{\text{OH}^-} \text{Kw}$  in Eq. 7 and  $k_{\text{Ox}} \text{K}_a$  in Eq. 8. In either case

$$k_{\text{M}} = 2 k_{\text{H}^+} + (\text{H}^+_{\text{M}}) \quad (\text{Eq. 9})$$

**Temperature Dependency of the Reactions.**—Velocity constants were determined at 37, 57, and 87° in acid solutions which were approximately 0.1, 0.2, and 0.4  $N$  with respect to hydrogen ion concentration. These measurements, which represent a type 2 reaction, were used to calculate the kinetic constants at 1  $N$  hydrogen ion concentration for each of the temperatures used. See Table II. The values obtained for the latter constant are:  $k_{\text{H}^+}$  at 37° =  $5.84 \times 10^{-4} \text{min.}^{-1}$ ;  $k_{\text{H}^+}$  at 57° =

$2.97 \times 10^{-3} \text{min.}^{-1}$ ; and  $k_{\text{H}^+}$  at 87° =  $2.98 \times 10^{-2} \text{min.}^{-1}$ . In Fig. 6, the velocity constants are plotted against the reciprocal of the absolute temperatures. The straight line relationship indicates that the mechanism responsible for the oxime hydrolysis is not altered with change in temperature. The relationship between temperature and velocity constants is shown by the Arrhenius equation

$$k_{\text{H}^+} = Z e^{-Ea/RT} \quad (\text{Eq. 10})$$

On calculating the slope and setting it equal to  $-Ea/2.303 RT$ , the energy of activation,  $Ea$ , was found to be approximately 17,400 calories per mole. The frequency factor in the Arrhenius equation,  $Z$ , was found by substituting the conditions at the three experimental temperatures. The average  $Z$  was found to be  $1.024 \times 10^9 \text{min.}^{-1}$ .

It is evident from Fig. 5 that above pH 4, the

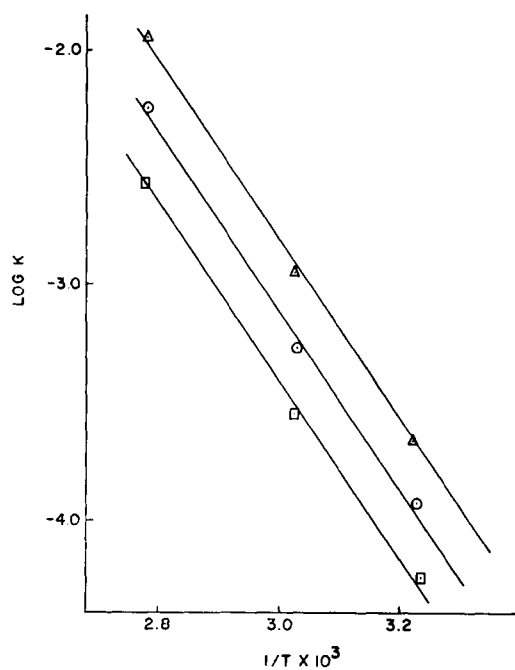


Fig. 6.—Temperature dependency of reaction 1 the hydrolytic reaction of 2-PAM, catalyzed by hydrogen ions, logarithm of  $k \text{min.}^{-1}$  plotted against the reciprocal of the absolute temperature.  $\Delta$ , 0.383  $N$ ;  $\circ$ , 0.191  $N$ ;  $\square$ , 0.096  $N$  perchloric acid.

overall reaction is essentially that of reaction 1. As the exact mechanism by which reaction 1 progresses has not been established, two energy of activation constants were determined, one for the potentially base catalyzed and one for the potentially uncatalyzed reaction. The logarithms of velocity constants for each mechanism, determined at pH values 5 to 13, were plotted against the reciprocals of the absolute temperature. Representative results, shown in Fig. 7, again indicate that neither mechanism for the dehydration reaction is altered with change in temperature. The average slope of the uncatalyzed reaction was found to be 6,200, the activation energy,  $E_a$ , being 28,500 calories per mole. The energy of activation of the base catalyzed reaction was found to be 17,000 calories per mole. By

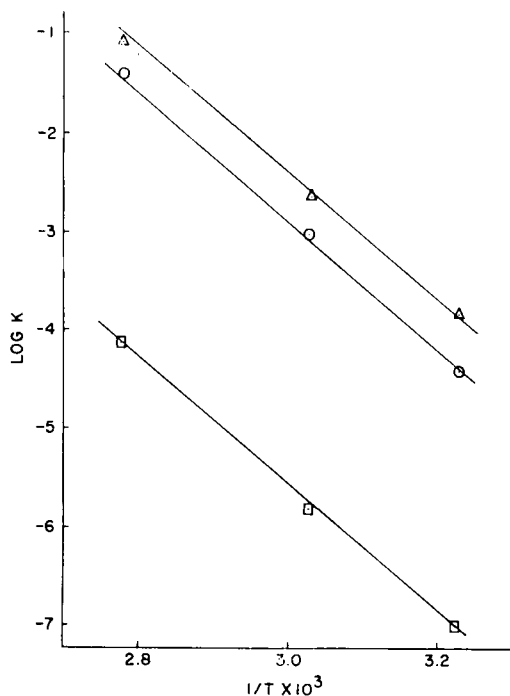


Fig. 7.—Temperature dependency of reaction 2, the dehydration reaction of 2-PAM at pH values 4, 7, and 10. □, pH 4; ○, pH 7; △, pH 10.

substituting the value of  $k_{Ox}$  and of  $k_{OH^-}$  at various experimental temperatures in the Arrhenius equation, the frequency factors come out to be  $1.797 \times 10^{16} \text{ min.}^{-1}$  and  $3.144 \times 10^{14} \text{ min.}^{-1}$ , respectively.

The overall equation for the breakdown of 2-PAM at various pH values is either

$$k = 1.02 \times 10^9 e^{-17,400/RT} (H^+) + 1.8 \times 10^{16} e^{-28,500/RT} \frac{K_a}{K_a + (H^+)} \quad (\text{Eq. 11})$$

or

$$k = 1.02 \times 10^9 e^{-17,400/RT} (H^+) + 3.1 \times 10^{14} e^{-17,000/RT} \frac{k_{OH^-} K_w}{K_a + (H^+)} \quad (\text{Eq. 12})$$

**pH of Minimum Hydrolysis.**—The hydrogen ion concentration at which minimum decomposition occurs is found at the point where the first term of the right-hand side of Eq. 11 or 12 equals the second term. On substituting into Eq. 8 the values of  $k_{H^+}$  and  $k_{Ox}$ , the equation for the pH of minimum decomposition  $pH_M$ , may be expressed as

$$pH_M = \frac{1}{2} \left( pK_a - 7.246 + \frac{2436}{T} \right) \quad (\text{Eq. 13})$$

The pH of minimum decomposition changes inversely with changes in temperature, ranging from 4.68 at 0° to 3.32 at 87° (Table III). The  $pK_a$  values at various temperatures may be estimated by substituting the corresponding experimental values into Eq. 4. As the  $pK_a$  values for 2-PAM were found experimentally to be between 7 and 8, the  $k_{H^+} (H^+)$  becomes small and may be eliminated. Thus

$$K_a = \frac{k_{H^+}}{k_{Ox} - k} \quad (\text{Eq. 14})$$

Using Eq. 11 or 12 the half-lives of 2-PAM can be calculated at any pH value and temperature. Predicted stability data over the region of pH 3 to 8 at temperatures from 10 to 87° are given in Table IV. The half-lives near the pH of minimum decomposition were, in most instances, extrapolated from initial rate constants as the half-lives are so long that experimental determinations were not practical.

**Equilibrium.**—In addition, we encountered in the acid region of pH 1 to 3, various conditions of equilibrium between 2-PAM and its hydrolysis products, pyridine - 2 - carboxaldehyde methiodide

TABLE IV.—PREDICTED STABILITY OF 2-PAM IN AQUEOUS SOLUTION,  $t_{1/2}$  (HALF-LIFE)

Temp., °C.	pH <sup>a</sup>					
	8	7	6	5	4	3
10	1.6 y	8.7 y	80 y	640 y	330 y	34 y
20	85 d	1 y	9 y	86 y	106 y	12 y
25	35 d	145 d	3.5 y	33 y	60 y	7 y
30	12 d	45 d	1 y	10 y	31 y	4.5 y
37	4.6 d	15 d	115 d	3 y	13.5 y	2.5 y
40	2.9 d	9.5 d	74 d	2 y	9 y	1.8 y
50	16 h	46 h	14.5 d	135 d	2.5 y	0.8 y
57	6 h	16 h	4.5 d	45 d	350 d	154 d
60	4 h	9.5 d	2.5 d	26 d	213 d	120 d
70	1.1 h	2.5 h	17 h	7 d	60 d	50 d
80	20 m	40 m	4.5 h	40 h	16 d	23 d
87	9 m	20 m	1.8 h	18 h	7 d	14 d

<sup>a</sup> y = years, d = days, h = hours, m = minutes.

(PCAM) and hydroxylamine. An equilibrium constant,  $k_{eq}$ , can be determined at any pH value. The equilibrium constant for reaction 2 is

$$k_{eq} = \frac{(\text{PCAM})(\text{NH}_2\text{OH})}{(2\text{-PAM})} \quad (\text{Eq. 15})$$

The basic dissociation constant for hydroxylamine may be arranged as

$$\frac{(\text{NH}_2\text{OH})}{(\text{NH}_3\text{OH})^+} = \frac{(\text{OH}^-)}{K_b} = \frac{K_w}{K_b(\text{H}^+)} \quad (\text{Eq. 16})$$

Substituting Eq. 16 into Eq. 15 and since the concentration of  $(\text{NH}_3\text{OH})^+$  is equal to the concentration (PCAM)

$$k_{eq} = \frac{K_w (\text{PCAM})^2}{K_b(\text{H}^+) (2\text{-PAM})} \quad (\text{Eq. 17})$$

The value of  $k_{eq}$  for the reactions in our study at 87° was approximately 20.

## REFERENCES

- (1) Wilson, I. B., and Ginsberg, S., *Biochim. et Biophys. Acta*, **18**, 168(1955).
- (2) Davies, D. R., and Green, A. L., *Discussions Faraday Soc.*, **20**, 269(1955).
- (3) Wills, J. H., Kunkel, A. M., Brown, R. V., and Groblewski, G. E., *Science*, **125**, 745(1957).
- (4) Askew, B. M., *Brit. J. Pharmacol.*, **12**, 340(1957).
- (5) Kewitz, H., Wilson, I. B., and Nachmansohn, D., *Arch. Biochem. Biophys.*, **64**, 456(1956).
- (6) Kondrizer, A. A., Ellin, R. I., and Edberg, L. J., *THIS JOURNAL*, **50**, 109 (1961).
- (7) Barrett, E., and Lapworth, A. L., *J. Chem. Soc.*, **93**, 85(1908).
- (8) Ambrose, D., and Brady, O. L., *J. Chem. Soc.*, **1950**, 1243.
- (9) Huckel, W., and Sachs, M., *Ann.*, **166**, 496(1932).
- (10) Acree, S. F., and Johnson, J. M., *Am. Chem. J.*, **38**, 308(1907).
- (11) Berger, M., and Brady, O. L., *J. Chem. Soc.*, **1950**, 1220.
- (12) Brady, O. L., and Jarett, S. G., *ibid.*, **1950**, 1232.
- (13) Vermillion, G., and Hauser, C. R., *J. Am. Chem. Soc.*, **63**, 1227(1950).
- (14) Reissert, R., *Ber.*, **41**, 3815(1908).
- (15) Brady, O. L., and Goldstein, R. F., *J. Chem. Soc.*, **1926**, 1918.
- (16) Ellin, R. I., *J. Am. Chem. Soc.*, **80**, 6588(1958).
- (17) Ellin, R. I., and Kondrizer, A. A., *Anal. Chem.*, **31**, 200(1959).

# Synthesis of Some N-Aralkyl-N-methylaminoethyl Carbanilates

By ROGER W. BARNES and WILLIAM J. ROST

In an attempt to correlate the basicity of local anesthetics with their activity, 21 substituted carbanilates of N-benzyl-N-methylaminoethanol, N-phenethyl-N-methylaminoethanol, and N-phenpropyl-N-methylaminoethanol were prepared. Substitutions on the carbanilic acid portion of the molecule were designed to study possible resonance effects. The compounds showed topical local anesthetic properties, but infiltration anesthetic properties were almost absent. No correlation between basicity and local anesthetic properties could be made. The relatively high acidity of the hydrochloride salts tested might account for the irritation commonly found.

CARBANILIC ACID esters of aminoalcohols have been reported to have marked local anesthetic activity (1, 2). Carbanilates with alkyl, chloro, amino, and alkoxy substitutions have been shown to possess a fair to high degree of local anesthetic activity (3-11). The position of the substitutions on the phenyl group have favorably affected the activity of the compounds in some cases (4, 6, 9). Sekera and Vrba have concluded that the more stable carbamates had a greater activity (6).

Aralkyl substitution on the nitrogen of aminoalkyl esters has given compounds with marked local anesthetic action. A 2% solution of  $\gamma$ -(2-benzylpiperidino)propyl benzoate or  $\gamma$ -(2-phenethylpiperidino)propyl benzoate gave a

corneal anesthesia lasting 5 to 6 days (12).  $\beta$ -(N-Methyl-N-phenethylamino)ethyl carbanilate administered intracutaneously to a guinea pig in 0.5% concentration, gave an anesthetic effect lasting more than 24 hours. The local anesthetic effect of this compound lasted 84 minutes when used on the rabbit cornea (13).

Because the aromatic substitutions gave a marked increase in the activity of dialkylaminoalkyl carbanilates and because N-aralkylation of the aminoalkyl benzoates, *p*-aminobenzoates, and the carbanilate proved effective, it was thought to be of interest to investigate the N-aralkylation of aminoalkyl esters of substituted carbanilic acids. Tolstouuhov has postulated that the local anesthetic effect of a molecule is related to the basicity of the amine nitrogen it contains (14). The N-aralkyl groups chosen for investigation were benzyl, phenethyl, and phenpropyl. The N substitutions might then vary the basic charac-

Received April 28, 1961, from the School of Pharmacy, The University of Kansas City, Kansas City 10, Mo.

Accepted for publication June 20, 1961.

Presented to the Scientific Section, A. P.H. A., Chicago meeting, April 1961.