Kinetics of the Decomposition of a Mannich Base

J. A. MOLLICA, J. B. SMITH, I. M. NUNES, and H. K. GOVAN

Abstract □ The elimination reaction of 3-(4-*o*-methoxyphenyl-1-piperazinyl)-4′-morpholinopropiophenone dihydrochloride (Su 17595A) was studied over the pH range of 1–10. It appears that only the unprotonated form of the Mannich base undergoes elimination in the pH range of 3–10. The observed rate constant for elimination as a function of pH corresponds well with the dissociation curve for the compound. The value $k_1 = 7.15 \times 10^{-2}$ min.$^{-1}$ (60°) was obtained for the specific rate constant for elimination. The elimination reaction is reversible, and the extent of reaction is also a function of pH because the reverse reaction, the addition of 1-(*o*-methoxyphenyl)-piperazine to 4′-morpholinoacrylophenone, proceeds only with the unprotonated amine. The reaction does not remain at equilibrium, because competitive (*e.g.*, desaminomethylation) and/or consecutive (*e.g.*, hydration and dimerization) reactions also can occur. In strong acid solution, the elimination of the protonated form is acid catalyzed.

Keyphrases □ Mannich base—decomposition kinetics □ 3-(4-*o*-Methoxyphenyl-1-piperazinyl)-4′-morpholinopropiophenone dihydrochloride—elimination reaction □ TLC—separation □ NMR spectroscopy—structure

An increasing number of publications have appeared on the synthesis of Mannich bases with potential therapeutic application, and a recent review in this journal discussed the mechanistic and technological considerations of the Mannich reaction (1). Although it has been long recognized that Mannich bases can be decomposed by steam distillation to yield an amine and an α,β-unsaturated ketone, few studies investigating this reaction in detail have been reported. Some workers have studied the elimination of β-morpholinopropiophenone over the pH range of 5.6–9 in their studies on the application of polarography to reaction kinetics (2–4).

Riviere (5), in his studies on the reversibility of the Mannich reaction, found that three processes may occur, depending upon the reaction conditions: (*a*) desaminomethylation or reverse Mannich reaction; (*b*) deamination or elimination; and (*c*) if a free amine is added to the reaction, amine exchange between the β-aminoketone and the amine.

Angeloni and Tramontini (6) and Andrisano *et al.* (7), in their studies on Mannich bases, investigated the decomposition of β-aminoketone hydrochlorides in boiling water and reported that the reaction follows pseudo-first-order kinetics under these conditions.

Koshy and Mitchner (8) reported on the acid-catalyzed hydrolysis of 2-(4-phenyl-1-piperazinyl methyl)-cyclohexanone hydrochloride (MA 1050). The reaction was studied over the pH range 1.1–5.5 and was found to be pseudo-first-order in nature and specific acid and general base catalyzed.

In this article the authors report on the decomposition reaction over the pH range of 1–10 for the Mannich base 3-(4-*o*-methoxyphenyl-1-piperazinyl)-4′-morpholinopropiophenone dihydrochloride (Su 17595A). This reaction is novel and interesting. Although simple pseudo-first-order kinetics were expected according to several reports (2–4, 6, 8), (at pH values less than the pKa), the authors did not observe them.

EXPERIMENTAL

Materials—Su 17595A, m.p. 208–211° dec., was used.[1] Purity of the compound was determined by phase-solubility analysis and by nonaqueous titration with perchloric acid in the presence of mercuric acetate. All material used in the kinetic studies had a minimum purity of 99% by both methods. 4′-Morpholinoacrylophenone, m.p. 88°, was prepared by elimination from 3-dimethylamino-4′-morpholinopropiophenone. The NMR spectrum had bands at 3.30 and 3.84 (8H, 2 multiplets); 6.90 and 7.90 (4H, 2 doublets); and the acrylic hydrogens at 5.8, 6.4, and 7.2.

Anal.—Calcd. for $C_{13}H_{15}NO_2$: C, 71.92; H, 6.95; N, 6.44. Found: C, 71.72; H, 6.93; N, 6.42. This material was used to confirm the reaction product found in solution and to check the specificity of the assay procedure.[2] The 1-(*o*-methoxyphenyl)-piperazine dihydrochloride, m.p. 220° dec., had a single trace impurity by TLC. All other chemicals used were of reagent grade.

Buffers—Reagent grade chemicals were used in the preparation of all buffer solutions. Solutions were prepared at an ionic strength of 0.1 or were adjusted to an ionic strength of 0.1 with potassium chloride. The following buffers were used: pH 1–2, hydrochloric acid; pH 3, formate; pH 4–6, acetate; pH 6–8, phosphate; and pH 9–10, borate.

Ionization Constants—The pKa values of Su 17595A were determined spectrophotometrically and potentiometrically. Spectrophotometric determination of the dissociation constants was conducted according to the procedure of Albert and Serjeant (9).

The values obtained spectrophotometrically at 25° are $pKa_2 = 1.04$ and $pKa_1 = 6.54$. A pKa_1 of 6.7 was determined at 25° by potentiometric titration with NaOH in water. A pKa of 9.0 was determined for 1-(*o*-methoxyphenyl)-piperazine at 25° by potentiometric titration with NaOH in water.

Equipment—The pH values were measured with a Radiometer model 25 SE meter using a K401 calomel electrode and a G202B glass electrode. The meter–electrode system was standardized against the standard buffers recommended by Bates (10). Standardization of the meter and determination of pH values were carried out at 60°. Potentiometric titrations to determine substance purity and ionization constants were performed with a Radiometer titrator type TTT1a and titragraph type SBR2c. Spectrophotometric measurements were made on a Beckman model DU, and spectra were obtained with a Cary model 11 or 14 spectrophotometer. Constant-temperature baths were maintained at 60 ± 0.05°.

Assay Development and Kinetic Procedure—Su 17595A can be determined by UV absorbance at 330 mμ. The 1-(*o*-methoxyphenyl)-piperazine has no absorbance at this wavelength; however, the 4′-morpholinoacrylophenone does absorb at 330 mμ and it is necessary to separate it from Su 17595A. An extraction procedure utilizing CCl_4–$CHCl_3$ (4:1) and 0.1 *N* H_2SO_4 was employed; the 4′-morpholinoacrylophenone is quantitatively extracted into the organic phase and the Su 17595A remains in the aqueous phase. Recovery studies of Su 17595A in mixtures containing up to a twofold excess of 1-(*o*-methoxyphenyl)-piperazine show that this decomposition product does not interfere in the extraction procedure. Recovery tests using up to a twofold excess of 4′-morpholinoacrylophenone show the unsaturated ketone to be completely extracted into the organic phase.

[1] The synthesis of compounds of this class has been reported by Dr. G. de Stevens, South African patent 6705,794(1968).

[2] The authors thank Dr. J. Bishop for providing this compound.

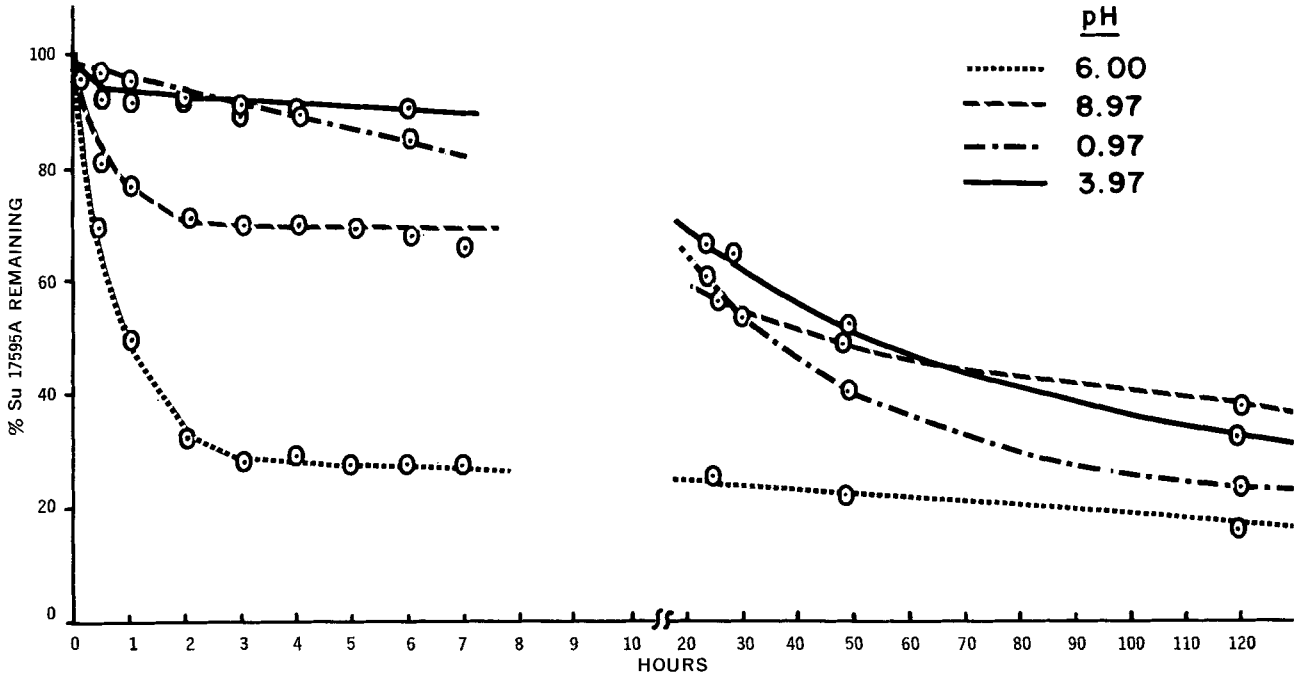


Figure 1—*Concentration of Su 17595A as a function of time at various pH values.* T = 60°.

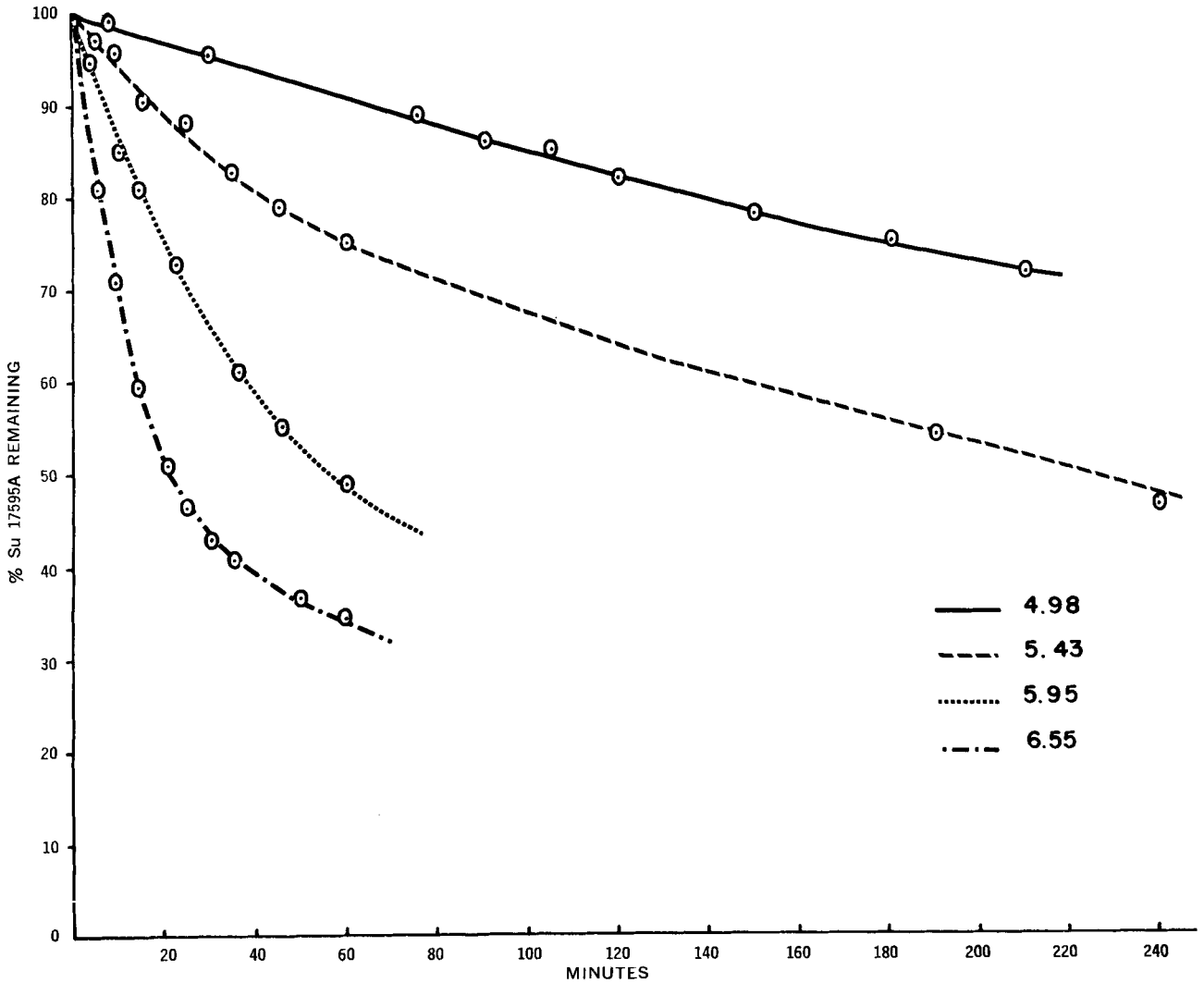


Figure 2—*Concentration* versus *time plots for the initial loss of Su 17595A at several pH values.* T = 60°; $C_0 = 4.15 \times 10^{-4}$ M.

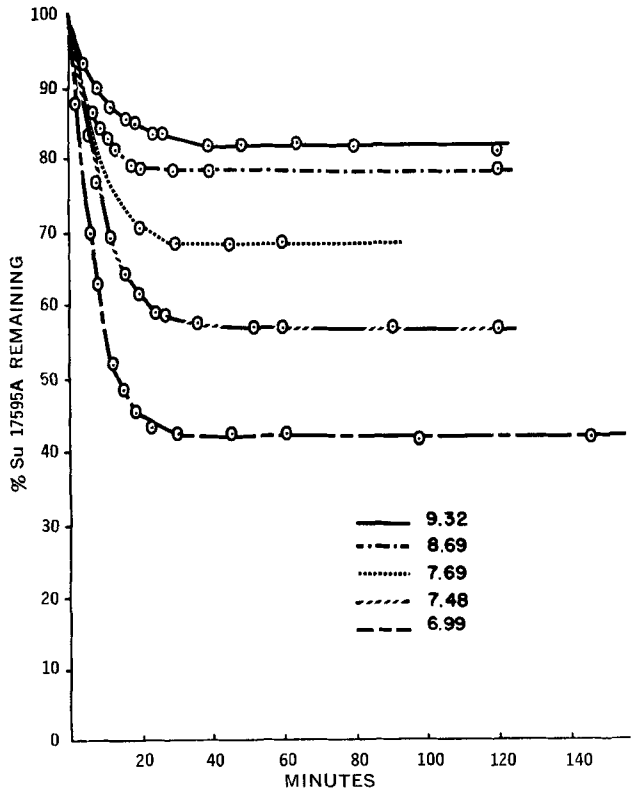
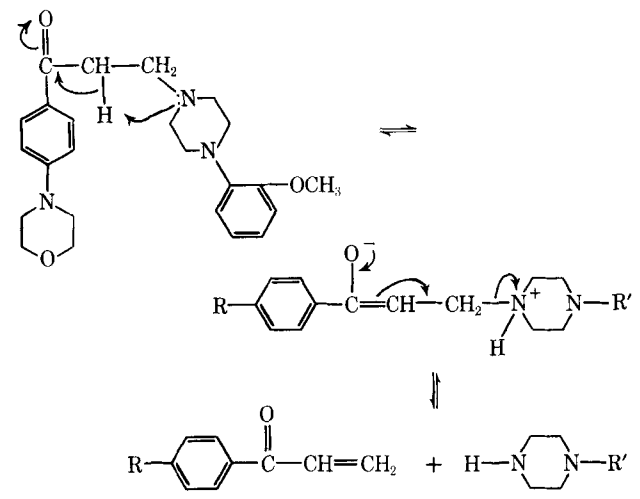


Figure 3—*Concentration* versus *time plots for the initial loss of Su 17595A and the attainment of equilibrium at several pH values.* T = 60°; $C_0 = 4.15 \times 10^{-4}$ M.

The following procedure was utilized throughout the study: a 20-mg. sample of Su 17595A was accurately weighed and transferred to a 200-ml. volumetric flask. To this was added 100 ml. of a buffer which had been equilibrated at 60°. The solution was rapidly mixed and placed in the 60° bath. A 5.0-ml. aliquot was transferred into a 125-ml. separator containing 15 ml. of the CCl_4–$CHCl_3$ solvent, 25 ml. of 0.1 *N* H_2SO_4, and sufficient 1 *N* H_2SO_4 to adjust the pH of the aqueous phase to a value of 1. The solution was cooled to room temperature to stop the reaction. The solution was shaken and the organic phase discarded. The extraction was repeated with three additional 15-ml. portions of CCl_4–$CHCl_3$; the aqueous layer was then filtered through cotton into a 50-ml. volumetric flask. The funnel was washed with two 5-ml. portions of 0.1 *N* H_2SO_4, and these washings were added to the volumetric flask. The solution was diluted to volume with 0.1 *N* H_2SO_4, and the absorbance was determined at 330 mμ against a 0.1 *N* H_2SO_4 blank.



Scheme I

Rate constants ($k_1^{obsd.}$) were obtained from the initial slopes of plots of log [Su 17595A] *versus* time and, in those instances where "equilibrium" was obtained, also from plots of

$$\log \left[\frac{1 - (1 - f_e)(1 - f)}{(1 - f) - (1 - f_e)} \right] \text{ versus } t$$

where f is the fraction reacted at the time t, and f_e is the fraction reacted at equilibrium.

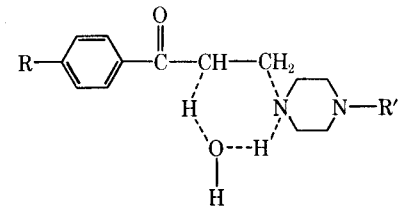
RESULTS AND DISCUSSION

The concentration *versus* time plots obtained were not amenable to simple interpretation. Figure 1 depicts the type of data obtained over a 5-day period. The reaction, in at least the intermediate pH region, appeared to approach a state of "quasiequilibrium," and the extent of reaction appeared to be a function of pH. Figures 2 and 3 show the initial loss of Su 17595A in the pH range of 4–9.

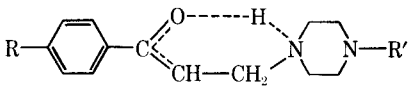
A mechanism consistent with such data indicates that only the unprotonated form of the Mannich base undergoes elimination and that only the unprotonated amine undergoes conjugate addition to the α,β-unsaturated ketone in the reverse reaction. It has been suggested (4) that in intermediate pH ranges, the elimination proceeds through intramolecular catalysis (Scheme I).

Analogous pathways, one of which incorporates a molecule of water, have been formulated using the two transition states, I and II.

Figure 4—*Plot of log* $k_1^{obsd.}$ versus *pH for elimination of Su 17595A. The points are experimental, and the solid line is a theoretical fit using the values in the text.*



I



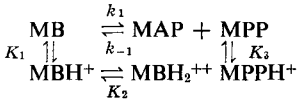
II

These two transition states would also give rise to the same products, and all three are kinetically indistinguishable.

The rate of loss of Su 17595A in accord with Scheme I can be expressed as follows:

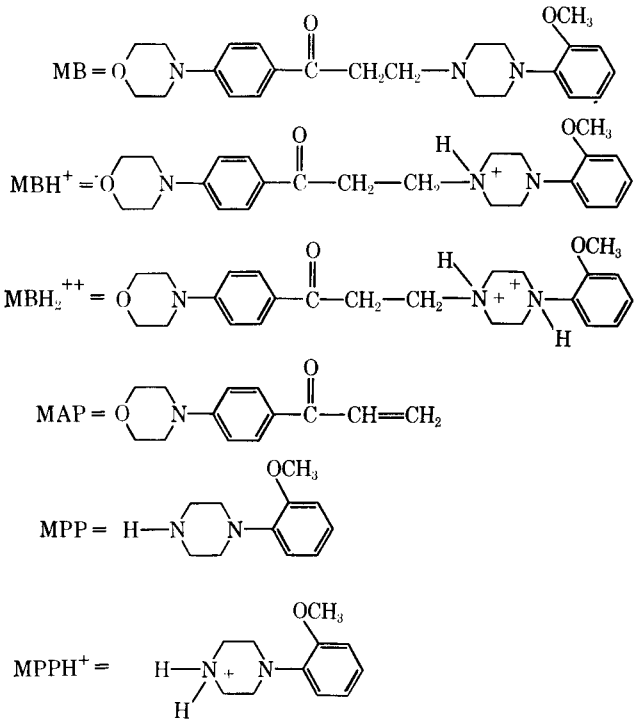
$$-d[MB_t]/dt = \frac{k_1[MB_t]}{1 + [H^+]/K_1} - \frac{k_{-1}[MAP][MPP]}{1 + [H^+]/K_3} \quad \text{(Eq. 1)}$$

where $[MB_t]$ = stoichiometric concentration of Su 17595A, [MPP] = stoichiometric concentration of 1-(*o*-methoxyphenyl)-piperazine, [MAP] = concentration of 4′-morpholinoacrylophenone, and the constants are as defined in Scheme II:



Scheme II

where



and K_1, K_2, and K_3 are the acid-dissociation constants; and k_1 and k_{-1} are rate constants for the forward reaction and reverse reaction, respectively.

The rate constant for the forward reaction (elimination reaction), $k_1^{obsd.}$, is given by the following equation:

$$k_1^{obsd.} = \frac{k_1}{1 + [H^+]/K_1} \quad \text{(Eq. 2)}$$

Figure 4 gives a plot of log $k_1^{obsd.}$ *versus* pH for the forward reaction.

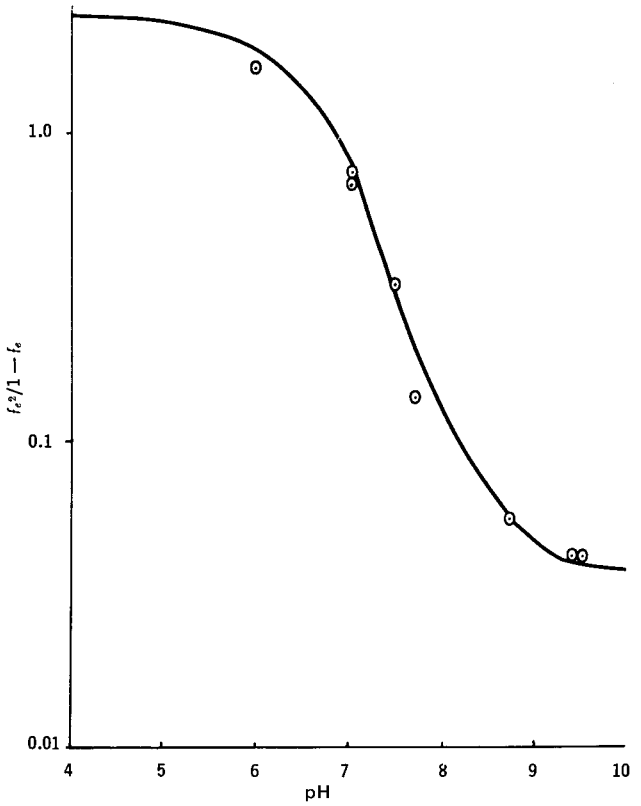


Figure 5—*Plot relating the fraction decomposed* (f_e) *to pH. The points are experimental, and the solid line is the theoretical line according to Eq. 3, using the following values:* $K_1 = 2.6 \times 10^{-7}$, $K = 1.5 \times 10^{-5}$, $K_3 = 4 \times 10^{-9}$, *and* $C_0 = 4.15 \times 10^{-4}$ M.

The solid line is drawn according to Eq. 2 using the values $k_1 = 7.15 \times 10^{-2}$ min.$^{-1}$, which is the average value calculated from the observed rate constants, and $K_1 = 2.6 \times 10^{-7}$, the dissociation constant, determined as described in the *Experimental* section. The experimental points, as can be seen, are in excellent agreement with the theoretical line.

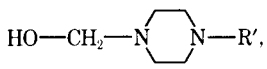
If Eq. 1 is operative and the predominant pathway for the reaction is as outlined, then at equilibrium one could write:

$$\frac{f_e^2}{1 - f_e} = \frac{K}{C_0} \cdot \frac{K_1}{K_3} \cdot \frac{[K_3 + [H^+]]}{[K_1 + [H^+]]} \quad \text{(Eq. 3)}$$

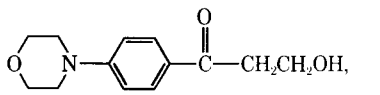
where f_e = fraction of Su 17595A decomposed at equilibrium, $K = k_1/k_{-1}$, K_1 and K_3 are as described previously, and C_0 = initial concentration of Su 17595A [*M*].

The extent of reaction was estimated from plots such as are given in Figs. 2 and 3, and the "equilibrium" values were plotted as a function of pH. As can be seen in Fig. 5, the values obtained from the initial plateau are in excellent agreement with the theoretical line according to Eq. 3. This lends further support to the hypothesis that at least the initial loss is primarily by this pathway.

The authors are not able to identify or isolate the amino alcohol,



in the reaction mixture. This would be the expected product of desaminomethylation or reverse Mannich reaction and has been reported by Riviere (5). The β-keto alcohol, which can arise from



the hydration of the α,β-unsaturated ketone, was detected in the reaction mixtures. The hydration and/or polymerization of the α,β-unsaturated ketone are the most likely driving forces which shift the equilibrium of the reaction.

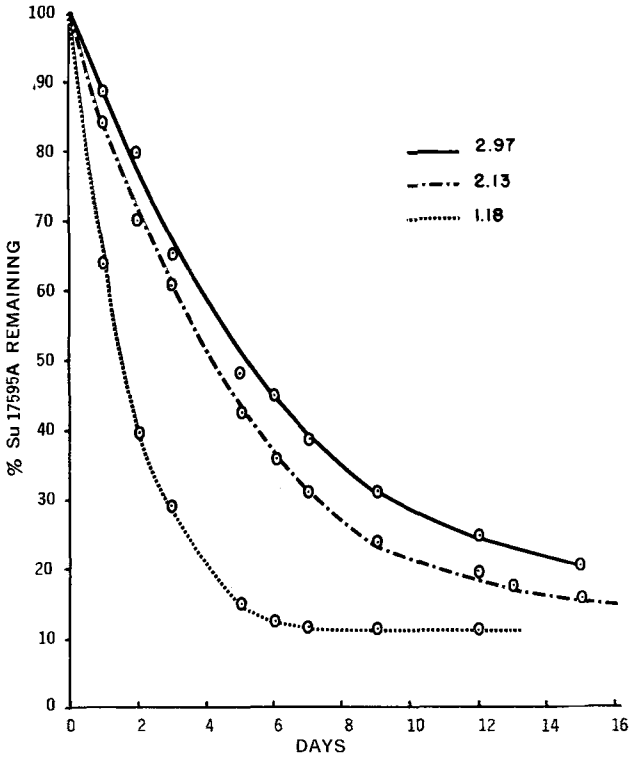


Figure 6—*Concentration* versus *time plots for the loss of Su 17595A in acidic solution.* T = 60°; $C_0 = 4.15 \times 10^{-4}$ M.

A kinetically equivalent scheme would be a bimolecular reaction involving hydroxide-ion catalysis of the protonated Mannich base. However, this would require a specific rate constant greater than 10^{-5} M^{-1} min.$^{-1}$, and one would expect significant buffer catalysis which was not observed.

In stronger acid solution (pH < 2), a mechanism consistent with the data could be as shown in Scheme III.

If there are no competitive or consecutive reactions, all equilibria shown in Scheme II would have to be satisfied. According to Eq. 1, even in solutions at pH 6 where the amine, 1-(*o*-methoxyphenyl)-piperazine, is completely protonated, the reaction does not go to completion. This can be seen in Fig. 6 where even at pH 1–2, 10–20% is still remaining at 10 days. (Equation 3 predicts a maximum of 80% degradation if only elimination is considered.)

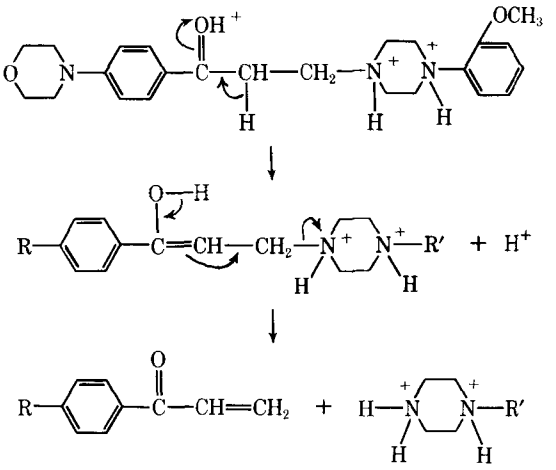
SUMMARY

1. Over a wide range of pH values, the principle route of decomposition appears to be elimination from the unprotonated Mannich base. These data are in excellent agreement with a theoretical curve constructed using the dissociation constant of the Mannich base.

2. This hypothesis is given further support in that the reversibility of the reaction is pH dependent and the extent of reaction can be correlated with the dissociation constant of the Mannich base. The reverse reaction, addition of the amine to the α,β-unsaturated ketone, can be correlated with the dissociation constant of 1-(*o*-methoxyphenyl)-piperazine.

3. Other pathways, such as desaminomethylation, are undoubtedly operative to a small extent as well as a bimolecular pathway for the elimination. The reaction is driven past equilibrium due to consecutive reactions of the α,β-unsaturated ketone such as hydration and dimerization.

4. In strong acid solution, hydrogen-ion catalysis of both the singly and doubly protonated forms (pk_2 = 1.04) is undoubtedly the major pathway.



Scheme III

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 23, 1970, from the *Development and Control Department, Ciba Pharmaceutical Company, Summit, NJ 07901*

Accepted for publication June 23, 1970.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, April 1970.