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CORRELATION OF THE BASE-CATALYZED DECOMPOSITION
RATES OF SOME BARBITURIC ACID DERIVATIVES WITH
SUBSTITUENT EFFECTS

DISSERTATION

Presented in Partial Fulfillment of the Requirements
for the Degree Doctor of Philosophy in the
Graduate School of The Ohio State
University

By

DONALD JOSEPH LAMB, B. Sc., M. Sc.

The Ohio State University
1960

Approved by:

[Signature]
Adviser
College of Pharmacy
ACKNOWLEDGMENTS

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I would like to acknowledge my wife, Virginia, for her kind consideration and encouragement throughout the preparation of this work.

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STATEMENT OF THE PROBLEM

It is generally known that the barbiturates, as a class of medicinals, are subject to decomposition in alkaline solution and that the rates of decomposition are affected by substituents. A search of the literature, however, reveals no systematic kinetic study to correlate the effects of structure on rate of decomposition. The purpose of this investigation was to determine the rates of base-catalyzed decomposition of a number of 5,5-disubstituted barbituric acid derivatives and to correlate the rates with Taft polar and/or steric constants of the 5-substituents. Steric constants, which were not available in the literature, were experimentally determined by synthesizing appropriately substituted acetic acids and measuring their rates of esterification in acidic media.
INTRODUCTION

The decomposition of 5-substituted barbituric acid derivatives in solution has been the subject of many reports\(^1\). These investigations were concerned with methods for evaluating the extent of decomposition and the identification of degradation products. A review of the literature lead Husa and Jatul\(^2\) to propose the following general pathway of decomposition.

\[ \text{For example see: L. Nielson, Dansk Tides Farm. 7, 137 (1933) through Quart. J. Pharm. and Pharmacol. 7, 130 (1934); W. J. O'Reilly and S. E. Wright, J. Pharm. and Pharmacol 6, 253 (1954); J. I. Bodin and A. Taub, J. Am. Pharm. Assoc. 44, 296 (1955).}\]

\[ \text{W. J. Husa and B. B. Jatul, J. Am. Pharm. Assoc. 33, 217 (1944).}\]
Tabern and Shelberg were the first workers to compare the stabilities of a series of 5-substituted barbiturates. Their results indicated that the stability was affected to a considerable degree by the nature of the substituents. They reported, for example, that a solution of sodium phenobarbital (5-ethyl-5-phenylbarbituric acid) was 96% decomposed in 16 hours at 100° while a solution of sodium pentobarbital (5-ethyl-5-(1-methylbutyl)-barbituric acid showed only 24% decomposition under the same conditions. They concluded that the barbiturates which possessed an -methyl group on a substituent showed marked stability toward alkaline hydrolysis. Their results are subject to question, however, since the experimental technique employed did not measure the cleavage of the barbiturate ring but rather the decarboxylation of the substituted malonuric acid formed.

The results of Fretwurst and Aspelund and co-workers also indicate the effect of substituents on the relative reactivities of

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4F. Fretwurst, Arzneimittel-Forschung 8, 44 (1955).
barbituric acid derivatives. Berggardh and Aspelund\(^7\) reported the unusual stability of ethyl-(1-methylbutyl)-barbituric acid towards alkaline hydrolysis as compared to its isomer, ethylisoamyl-barbituric acid. The results of these investigations indicate that the substituents of the barbituric acid derivatives greatly influence the reactivity of these compounds toward alkaline hydrolysis. They do not, however, indicate the properties of structure responsible for this substituent effect. Furthermore, studies of this type do not give adequate information from which a reaction mechanism can be postulated.

The science of chemical kinetics provides the best general method for determining the mechanism of reaction\(^8\). It was not until recently that well controlled kinetic studies were utilized to investigate degradative reactions of barbiturates. Hasegawa and co-workers\(^9\), for example, investigated the hydrolysis of phenobarbital. They reported the reaction to be specific base-catalyzed and postulated a mechanism which resembled that for ester hydrolysis. Kostenbauder\(^10\), on the other hand, found the decomposition of phenobarbital to be general base-catalyzed. He stated that the mechanism of this reaction was more complicated than the one assigned to the hydrolysis of esters. Autian and co-workers\(^11\) reported

\(^7\)C. Berggardh and H. Aspelund, Finska. Kenistsamfundets Medd. 59, 64 (1950), through Chem. Abs. 47, 1607 (1953).


\(^10\)H. B. Kostenbauder, Private Communication.

that the decomposition of secobarbital was catalyzed by general acids and bases. Autian and co-workers\textsuperscript{12} also studied the kinetics of barbital decomposition in an ammonia buffer system. They found a catalytic contribution to the rate of reaction by hydroxide ion and ammonia but not hydrogen ion. They suggested that the reaction of ammonia with barbital may be similar to ammonolysis of an ester. The apparent lack of hydrogen ion catalysis was attributed to the weakly basic nature of the imide structure of barbital.

The variation in reactivity within a class of organic compounds may be attributed to the polar, steric, and resonance effects of the substituents on the functional group\textsuperscript{13}. These effects may vary separately or simultaneously as structure is varied in a reaction series. A quantitative method for separating these effects is needed, therefore, before the influence of substituents can be accurately described. Ingold\textsuperscript{14} proposed a method for separating the polar and steric effects in ester hydrolysis rates. He stated that since the steric effects should be about the same for acid- and base-catalyzed reactions, the ratio of rate constants, $k_B/k_A$, of base- to acid-catalyzed hydrolysis should be a function only of the polarity of the substituent. This proposal lead Taft to develop the following equation for evaluating the polar effect of substituents on the rates of ester hydrolysis\textsuperscript{15}:

\begin{equation}
\frac{k_B}{k_A} = \alpha + \beta \cdot [A]_0
\end{equation}


2.48

\[ \sigma^* = \frac{1}{2.48} \left[ \log (k/k_0)_B - \log (k/k_0)_A \right] \] (1)

* is the polar substituent constant. \( k_0 \) and \( k \) are the rate constants for hydrolysis of the acetate ester (the standard of comparison) and the substituted acetic acid ester respectively. The subscripts A and B refer to the acidic and basic hydrolysis conducted under the same conditions of solvent and temperature. The resonance effects of substituents on the alkaline and acidic hydrolysis rates of esters should also be constant. The proposed transition states for both reactions are saturated and thus preclude conjugation between the substituents and the functional group. Taft found that both rates and equilibria could be correlated for reactants of the type R-Y by the equation

\[ \log (k/k_0) = \sigma^* \rho^* \] (2)

where \( \rho^* \) is the polar reaction constant and is a measure of the susceptibility of a particular reaction series to polar effects of the substituents. The factor, \( k_0 \), again refers to the rate constant of the methyl substituted reactant as standard of comparison. It is a necessary prerequisite or a foregone conclusion for a correlation of this type that a single mechanism is consistent in a reaction series. The sign of the polar constant and also the reaction constant is significant. A substituent having a positive value of \( \sigma^* \) identifies it as an electron withdrawing group. If the value of \( \sigma^* \) is negative the substituent is electron donating. A positive reaction constant, \( \rho^* \) indicates that the reactivity of the functional group common to the reaction series is

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increased by electron withdrawing groups. A negative value of $\rho^*$ indicates the opposite.

The variety of reaction series which can be described by equation 2 is seen in the following examples taken from the list compiled by Taft: the ionization of carboxylic acids, $\text{RCOOH}$; the hydrolysis of diethyl monosubstituted acetals, $\text{RCH(O\text{C}_2\text{H}_5)}_2$; carbon-oxygen stretching spectra for alcohols, $\text{ROH}$; polarigraphic reduction of $\alpha$-bromoacetic acids, $\text{R}_1\text{R}_2\text{C(Br)CO}_2\text{H}$; and solvolysis of tertiary alkyl halides, $\text{R}_1\text{R}_2\text{R}_3\text{CCl}$. The additive nature of the polar constants is illustrated by the last two examples. Thus the total polar contribution of several substituents can be obtained by summing the polar constants of the individual substituents. The examples also show that physical as well as chemical properties can be correlated with substituent constants.

Taft was also successful in isolating the steric effect of substituents on reactivity. He noted that the relative rates of the acid-catalyzed esterification of substituted acetic acids or the acid-catalyzed hydrolysis of their esters were virtually free of polar effects of the substituents. He concluded that these relative rates were a near-quantitative measure of the steric effects of the substituents. This conclusion was stated in the form of an equation given by

$$\log (k/k_0)_A \equiv E_s$$

(3)

where $E_s$ is the steric substituent constant. These $E_s$ values were determined from the relative rates, $k/k_0$ of the substituted acetic acid to acetic acid itself in the esterification reaction or $k/k_0$ of the sub-

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stituted acetic acid ester to acetate ester in the hydrolysis reaction. He found that in those reaction series where polar effects were negligible the reactivity of the members could be correlated with $E_8$ values by the equation:

$$\log \left( \frac{k}{k_0} \right) = \delta E_8$$  \hspace{1cm} (4)

where $\delta$ is the steric reaction constant and is a measure of the susceptibility of the reaction series to the steric requirements of the substituents. The $E_8$ values, unfortunately, are not additive functions of structure. The steric constant for each substituent, therefore, must be experimentally determined.

A more critical test of the separation of polar and steric substituent effects was recently reported by Pavelich and Taft. They investigated the sodium methoxide-catalyzed methanolysis of $\alpha$-menthyl esters of alkane carboxylic acids and found that rates of reaction in this series were dependent on both $\rho^*$ and $E_8$ values. They showed that the variation in reactivity could be quantitatively correlated with these values by the equation:

$$\log \left( \frac{k}{k_0} \right) = \sigma^* \rho^* + \delta E_8$$  \hspace{1cm} (5)

where all of the symbols have the same significance as before. Excellent agreement was found between the $\rho^*$ value of this reaction series and the one obtained from a reaction series where steric effects were negligible. The presence of a second adjustable parameter, $\sigma$, in equation 5, therefore had no apparent influence on the value of $\rho^*$ obtained.

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The converse was also found to be true. The presence of a polar parameter in equation 5 had no effect on $\delta$, as shown by the agreement of this value (+1.301) with the steric reaction constant for the acid-catalyzed methanolysis of $\beta$-naphthyl esters of aliphatic carboxylic acids ($\delta = +1.376$). Polar effects of substituents, as previously mentioned, are negligible in the acid-catalyzed lysis of esters.

These methanolysis reactions were shown by kinetic methods to involve acyl-oxygen fission with a mechanism analogous to normal ester hydrolysis. The authors point out that the agreement of the reaction constants in sign and magnitude was further evidence of this mechanism.

The purpose of this study is to determine the rates of base-catalyzed decomposition of a number of 5,5-disubstituted barbituric acids and to correlate these rates with the Taft polar and/or steric constants of the 5-substituents. This quantitative correlation would be useful in several respects: (a) the existence of the correlation would indicate a consistency in reaction mechanism, (b) the reaction constants, if in agreement with those for the methanolysis of esters, would corroborate the assumption that the mechanism of phenobarbital decomposition is similar to ester hydrolysis, (c) the rates of decomposition of barbiturates not included in this series could be estimated from their substituent constants.

The substituted barbituric acids studied have pKa values in the region of 8.0 ± 0.05. In aqueous solution at a pH of 10 or greater they would exist mainly in the form of their enolized conjugate bases. Below pH 10, however, appreciable amounts of the undissociated acid would be present in solution. A rate expression for the decomposition
of these compounds, therefore, must account for the species present under the experimental conditions.

At constant hydroxide ion concentration and at pH values below 10 the rate of reaction is given by

$$\frac{-d(HA)_T}{dt} = k(HA) + k'(A)$$

where \((HA)_T\) is the total concentration of acid. \((HA)\) and \((A)\) represent the concentrations of unionized and ionized acid respectively. If the unionized acid does not react or its rate of reaction is negligible compared to \(A\), then,

$$\frac{-d(HA)_T}{dt} = k' (A)$$

The concentration of the anion can be calculated by considering \(\alpha\) the degree of ionization of the acid. Thus the rate expression can be modified to be:

$$\frac{-d(HA)_T}{dt} = k' \alpha (HA)_T$$

where \(\alpha = \frac{K_a}{K_a (H_3O^+)}\)

It is apparent from equations 7 and 8 that at pH values above 10, \(k'\) the specific rate constant for the anion will be equal \(k_{obs}\) the observed rate constant. However, at pH values below 10, \(k' = k_{obs}/\alpha\).

If the decomposition of the anion is subject to catalysis by other bases in addition to hydroxide ion, \(k_{obs}\) is a composite of catalytic constants for the various species contributing to the decomposition.
This term may be separated into its component terms by the equation:

$$k_{obs} = k_0 + S k_i B_i$$  \hspace{1cm} (9)$$

where $k_0$ is the rate constant of the "spontaneous" reaction or the contribution of the water molecule to the hydrolytic rate and the second term represents the summation of the catalytic contributions of the basic species present in solution. In this study the hydroxide ion and the basic component of the buffer pair are the catalytic species present and thus equation 9 becomes

$$k_{obs} = k_0 + k_{OH}(OH) + k_E(E)$$  \hspace{1cm} (10)$$

where $k_{OH}$ and $k_E$ are the specific catalytic constants for catalysis by the hydroxide ion and the basic buffer component respectively. If only specific hydroxide ion catalysis is indicated equation 10 reduces to

$$k_{obs} = k_{OH}(OH)$$  \hspace{1cm} (11)$$

The complete rate equation for the decomposition of the barbituric acid derivative will then be

$$\frac{-d(HA)_T}{dt} = \sqrt{k_0 + k_{OH}(OH)} \alpha (HA)_T$$  \hspace{1cm} (12)$$

Similarly, if catalysis by both the hydroxide ion and the basic buffer component are observed, the rate will be described by

$$\frac{-d(HA)_T}{dt} = \sqrt{k_0 + k_{OH}(OH) + k_E(E)} \alpha (HA)_T$$  \hspace{1cm} (13)$$

The specific rate constant $k_E$ can be determined by measuring the rate of decomposition at several buffer concentrations but at constant ratio of base to salt and constant ionic strength. Under these conditions the hydroxide ion should be constant. If the reaction is first-order a
plot of $k_{obs}$ vs. ($E$) should be a straight line with a slope equal to $k_g$ and an intercept of $\overline{k_o} + k_{OH}(OH)^{-}$. The value of $k_{OH}$ can be obtained by measuring the rate of reaction in a series of solutions containing varying concentrations of hydroxide ion. According to equation 11 a plot of $k_{obs} - k_g(E)$ versus (OH) should be linear if the reaction is first order. The slope of this line will equal $k_{OH}$ and its intercept should give $k_o$. If the hydroxide ion concentration decreases to a level where an appreciable amount of the barbiturate is in the form of the undissociated acid the above plot will not be linear. However, a plot of $k_{obs}/\alpha - k_g(E)$ versus (OH) should be linear and the slope and intercept will be equal to $k_{OH}$ and $k_o$ respectively.
EXPERIMENTAL

I Determination of the Rates of Base-Catalyzed Decomposition of Selected Barbiturates

Materials

The barbiturates were purified by recrystallization from ethanol-water mixtures with the exception of butethal which was recrystallized from a mixture of ether and petroleum ether. All had melting ranges of less than one degree and these ranges agreed with literature values. A stock solution of ethanolamine base was prepared from Eastman-Kodak "white label" material and demineralized double-distilled water and stored in a polyethylene bottle. The stock bottle was protected from carbon dioxide with soda lime tubes and the solution was dispensed under nitrogen pressure. The solution was standardized by titration with standard hydrochloric acid using methyl red indicator. The standard hydrochloric acid solution was used with the ethanolamine solution to prepare the buffer mixture in situ. A standard solution of potassium chloride obtained from the Reagent Laboratory of the Laboratory Supply Stores was used to adjust the ionic strength of the buffer solutions.

pH Measurements

The pH values of the buffered barbiturate solutions used in the kinetic runs were determined at the temperature of the study using a Beckman Model GS pH Meter and the A scale of the instrument. The pH cell consisted of a 180 ml. electrolytic beaker equipped with a rubber

stopper. Holes were drilled into the stopper to accommodate a Beckman "general purpose" glass electrode, a calomel electrode, inlet and outlet tubes for nitrogen, and an Anschuetz thermometer calibrated by the National Bureau of Standards. The pH meter was standardized at the desired temperature with Beckman Buffer No. 3581, diluted according to directions. All solutions for standardization and testing were quillibrated at the desired temperature before use. A slow stream of nitrogen was passed through a presaturator containing distilled water at the temperature of the test and then through the test solution during the pH measurement. The compensator dial was set at 25° and the buffer setting and pH reading at the desired temperature of the solution were used to calculate the pH of the solution according to the instruction manual furnished with the instrument. The pH value of each test solution was also measured at room temperature before and after the kinetic run to determine whether the pH remained constant. In all instances the two measurements agreed within experimental error.

**Kinetic Measurements**

A sample of barbiturate sufficient to yield a concentration of approximately $2 \times 10^{-3}$ molar was weighed into a glass-stoppered volumetric flask. An amount of standard sodium hydroxide solution required to neutralize 95% of the acid was added and the mixture agitated until all of the solid dissolved. A calculated volume of the ethanolamine, hydrochloric acid, and potassium chloride stock solutions was then added to obtain the desired acid-base buffer ratio and constant ionic strength in the final solution. The solution was then made up to volume with demineralized double-distilled water. The ionic strength was kept constant
at 0.2 throughout all the kinetic runs. The total concentration of ethanolamine used was 0.2 molar in all of the rate studies except in those which were designed to investigate the possibility of general-base catalysis.

Two milliliters aliquots of the solution were placed in 2 ml. Neutra-glas ampoules with the aid of a hypodermic syringe. The ampoules were sealed and placed in wire baskets supported in a Sargent Thermoniter Constant Temperature Bath containing Light Mineral Oil U.S.P. The glass bath was insulated against heat loss by placing it in an empty soap drum cut to the appropriate height and filling the space between the glass and drum with glass wool. The top was then covered with the drum lid which was provided with a hole for a thermometer. Using this device a temperature control of ±0.02° at 60° and ±0.05° at 75° could be obtained. Five minutes was allowed for the ampoules to reach bath temperature before timing of the reaction was begun. This equilibration time was established by placing a test tube containing 2 ml. of distilled water and a thermometer in the bath noting the time necessary for the water to reach the temperature of the bath. At various time intervals, ampoules were removed from the bath and plunged into a chloroform-dry ice mixture. The contents of the ampoule froze immediately and were stored in this condition in the freezing compartment of a refrigerator until the time of assay.

To determine whether any decomposition of barbiturate occurred while in the frozen state, several ampoules of freshly prepared barbital solution were stored in the freezer for two weeks. No decomposition occurred.
The decomposition of the barbiturates was followed by assaying the ampoule contents spectrophotometrically for undegraded barbiturate. Eight to ten ampoules were used in each kinetic run. The frozen ampoules were allowed to warm to room temperature and a 1 ml. aliquot of the solution was removed and placed in a 25-ml. glass-stoppered flask. The solution was then diluted to the mark with pH 10.9 phosphate buffer. The absorbancy of this solution was determined in a Beckman DU Spectrophotometer at the wavelength of maximum absorption of the barbiturate under investigation. Matched 1 cm. silica cells were used and the phosphate buffer served as a blank solution.

A plot of the logarithm of the absorbancy versus time in hours was found to be linear up to 65% reaction for all the barbiturates studied. The equation for the best line through the experimental points was obtained by the method of least squares (Appendix I). The estimating equation for this method is given by

\[ \log A_t = \log A_0 + (\text{slope}) \ t \quad (14) \]

where \( \log A_t \) is the logarithm of the optical density at time, \( t \), and \( \log A_0 \) is the intercept. The pseudo-first-order rate constants were calculated from the relationship

\[ k_{\text{obs}} = -2.303 \ (\text{slope}) \quad (15) \]

and have the dimensions of hours\(^{-1}\).

The results for the decomposition of allyl barbituric acid at 75° and pH 9.03 serve as a typical example of this procedure. Figure 1

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illustrates the linear relationship between log $A_t$ and time. The equation for the best line through the experimental points was calculated to be

$$\log A_t = -0.1131 - 0.00423t$$  \hspace{1cm} (16)

and, therefore, from equation 15

$$k_{obs} = -2.303 (-0.00423) \times 0.00974 \text{ hours}^{-1}$$

The agreement between the experimentally determined values of log $A_t$ and those calculated by equation 16 is shown in Table 1. The observed rate constants for the decomposition of the selected barbiturates at two temperatures and their standard deviations are listed in Table 2.

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>-log $A_t$ (obsd)</th>
<th>-log $A_t$ (calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.9</td>
<td>0.269</td>
<td>0.278</td>
</tr>
<tr>
<td>47.6</td>
<td>0.312</td>
<td>0.315</td>
</tr>
<tr>
<td>62.0</td>
<td>0.379</td>
<td>0.376</td>
</tr>
<tr>
<td>65.9</td>
<td>0.396</td>
<td>0.392</td>
</tr>
<tr>
<td>71.8</td>
<td>0.426</td>
<td>0.417</td>
</tr>
<tr>
<td>82.2</td>
<td>0.461</td>
<td>0.461</td>
</tr>
<tr>
<td>90.3</td>
<td>0.496</td>
<td>0.495</td>
</tr>
<tr>
<td>94.7</td>
<td>0.511</td>
<td>0.514</td>
</tr>
<tr>
<td>108.1</td>
<td>0.568</td>
<td>0.571</td>
</tr>
<tr>
<td>117.7</td>
<td>0.607</td>
<td>0.611</td>
</tr>
</tbody>
</table>
Fig. 1. A plot showing the linear relationship between \( \log A_t \) and time. The circles are the experimental values and the line was calculated from equation 16.
Table 2. Observed Rate Constants for the Decomposition of the Selected 5,5-substituted Barbituric Acids at Two Temperatures

<table>
<thead>
<tr>
<th>5,5-substituted Barbituric Acid</th>
<th>$k_{obs} \times 10^2$ (Hr.⁻¹)</th>
<th>60°, pH 9.19</th>
<th>75°, pH 9.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diallyl</td>
<td>2.27 ± 0.03</td>
<td>7.86 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Diethyl</td>
<td>0.538 ± 0.009</td>
<td>2.20 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Ethyl-n-butyl</td>
<td>0.429 ± 0.009</td>
<td>1.83 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Ethylisooamyl</td>
<td>0.411 ± 0.006</td>
<td>1.70 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Phenylethyl</td>
<td>0.625 ± 0.007</td>
<td>1.61 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Allylisobutyl</td>
<td>0.232 ± 0.005</td>
<td>0.97 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Allylisopropyl</td>
<td>0.046 ± 0.001</td>
<td>0.213 ± 0.004</td>
<td></td>
</tr>
<tr>
<td>Ethyl-sec-butyl</td>
<td></td>
<td>0.091 ± 0.001</td>
<td></td>
</tr>
<tr>
<td>Ethyl-(1-methylbutyl)</td>
<td>0.076 ± 0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylisopropyl</td>
<td></td>
<td>0.084 ± 0.003</td>
<td></td>
</tr>
</tbody>
</table>

*a* This compound was only 9% decomposed in 16 days at 60°

The effect of the hydroxide ion concentration on the rate of decomposition of barbital and diallyl barbituric acid was investigated at 75°. The concentration of barbiturate and total ethanolamine was maintained constant but different amounts of standard hydrochloric acid were added to the test solutions. The pH of each solution was measured at 75°. The hydroxide ion concentration was calculated from the pOH which in turn was obtained by subtracting the pH from the thermodynamic pKw. Concentration and activity were assumed equivalent in the dilute solutions used. The pKw was calculated to be 12.70 at 75° from the equation

$$\log Kw = -4470.99 + 6.0875 - 0.017069 \frac{T}{T}$$

The observed rate constants obtained at the various hydroxide concentrations are listed in Tables 3 and 4.

---

The effect of buffer concentration on the rate of decomposition of barbital and diallyl barbituric acid at 75° was also investigated. In these studies, the buffer concentration was varied by adding different quantities of ethanolamine stock solution to separate flasks containing equal amounts of the barbiturate. The hydroxide ion concentration was kept constant by adding a quantity of hydrochloric acid solution calculated to maintain a constant salt/base buffer ratio of one-third in each test solution. The ionic strength was kept constant by the addition of potassium chloride solution. The pH of the test solutions for each compound was the same within experimental error. The observed rate constants for these kinetic runs are listed in Table 5 with \((E)^T\), the total concentration of ethanolamine, and \((E)\), the concentration of ethanolamine free base.

Table 3. The Observed Rate Constants for the Decomposition of Barbital at Various Hydroxide Ion Concentrations at 75°

<table>
<thead>
<tr>
<th>((\text{OH}) \times 10^4) (Moles/Liter)</th>
<th>(k_{\text{obs}} \times 10^2) (Hr.(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.22</td>
<td>1.77 ± 0.04</td>
</tr>
<tr>
<td>0.47</td>
<td>1.91 ± 0.02</td>
</tr>
<tr>
<td>0.87</td>
<td>1.99 ± 0.05</td>
</tr>
<tr>
<td>2.1</td>
<td>2.20 ± 0.05</td>
</tr>
<tr>
<td>4.9</td>
<td>2.42 ± 0.05</td>
</tr>
</tbody>
</table>
Table 4. The Observed Rate Constants for the Decomposition of Diallyl Barbituric Acid at Various Hydroxide Ion Concentrations at 75°

<table>
<thead>
<tr>
<th>(OH) x 10^4 (Moles/Liter)</th>
<th>k_{obs} x 10^2 (Hr.(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21</td>
<td>5.42 ± 0.07</td>
</tr>
<tr>
<td>0.45</td>
<td>6.11 ± 0.03</td>
</tr>
<tr>
<td>0.66</td>
<td>6.56 ± 0.09</td>
</tr>
<tr>
<td>2.1</td>
<td>7.90 ± 0.09</td>
</tr>
<tr>
<td>4.8</td>
<td>10.21 ± 0.05</td>
</tr>
</tbody>
</table>

Table 5. Observed Rate Constants for the Degradation of Barbital and Diallyl Barbituric Acid at Various Buffer Concentrations at 75°

<table>
<thead>
<tr>
<th>(E) (_p) (Moles/Liter)</th>
<th>(E) (Moles/Liter)</th>
<th>k_{obs} x 10^2 (Hr.(^{-1})) Barbital (pH 9.03)</th>
<th>Diallyl Barbituric Acid (pH 9.00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5014</td>
<td>0.3761</td>
<td>2.10 ± 0.07</td>
<td>8.13 ± 0.07</td>
</tr>
<tr>
<td>0.4011</td>
<td>0.3009</td>
<td>2.16 ± 0.04</td>
<td>7.98 ± 0.06</td>
</tr>
<tr>
<td>0.3009</td>
<td>0.2256</td>
<td>2.16 ± 0.04</td>
<td>7.83 ± 0.07</td>
</tr>
<tr>
<td>0.2006</td>
<td>0.1507</td>
<td>2.16 ± 0.04</td>
<td>7.83 ± 0.07</td>
</tr>
<tr>
<td>0.1003</td>
<td>0.0752</td>
<td>2.15 ± 0.03</td>
<td>7.42 ± 0.03</td>
</tr>
</tbody>
</table>
II Synthesis of Substituted Acetic Acids

The substituted acetic acids were prepared from the corresponding diethyl malonates by saponification and decarboxylation. Diethyl ethyl-isoamylmalonate and diethyl diallylmalonate were purchased commercially. The remainder of the malonates were synthesized from diethyl ethylmalonate or diethyl allylmalonate by the method of Wallingford and co-workers\(^\text{22}\). None of the products of the several steps were isolated or purified except the desired substituted acetic acid. The synthesis of ethyl-(1-methylbutyl)-acetic acid serves as an example of the method used to prepare the acetic acid derivatives from a monosubstituted malonate.

A 6.1 g. (0.27 mole) sample of clean sodium metal was added to approximately 200 ml. of commercial absolute ethanol in a three-neck, one-half liter flask equipped with a condenser and a ball and socket-type stirrer. The third opening was closed with a ground-glass stopper. The mixture was stirred and the flask cooled with an ice bath until all of the sodium metal dissolved. The condenser was then replaced by a distilling head connected to an adapter and flask. The excess alcohol was then removed by distillation under reduced pressure at the water pump. A water bath was used to warm the flask during distillation. Fifty grams (0.27 mole) of diethyl ethyl malonate and 160 ml. (5 molar equivalent excess) of diethyl carbonate was added to the dry sodium ethoxide remain-

ing in the flask. The mixture was stirred at room temperature until
the solid was completely dissolved. An electrically heated fractionat-
ing column of 13 mm I. D. and packed throughout a length of 44 cm. with
glass helices and bearing a controllable take-off head was connected to
the flask. The alcohol present from the sodium ethoxide and any formed
while heating the mixture was removed under reduced pressure (150 mm.).
The flask was allowed to cool to room temperature and the fractionating
column was replaced with a dropping funnel. A 44.2 g. sample (10% molar
excess) of 2-bromopentane was added through the dropping funnel over a
45 minute period. After addition of the halide the well stirred mixture
was slowly heated to 100° and held in this region until only slightly
alkaline to phenolphthalein (60 hours). A white precipitate began to
form when the temperature of the mixture reached 60°. The reaction
mixture was allowed to cool to room temperature and an equal volume of
water and 1 ml. of glacial acetic acid was added to the flask. The pre-
cipitate dissolved immediately. The two phases were then transferred
to a separatory funnel and the diethyl carbonate layer was drawn off.
The water layer was extracted with three 100 ml. portions of isopropyl
ether. The combined extracts and the diethyl carbonate layer were
extracted twice with small portions of saturated salt solution and fil-
tered through anhydrous magnesium sulfate. The ether was removed from
the solution with a film evaporator and the diethyl carbonate by dis-
tilling through the fractionating column under reduced pressure.
Eighty-eight grams (5 molar equivalent excess) of 85% potassium hydro-
oxide and 300 ml. of alcohol were added to the viscous liquid remaining
in the flask after removal of the solvent. The mixture was refluxed on a steam bath for 24 hours during which time a solid precipitated. One hundred ml. of water was added to the hot solution and the alcohol was removed by distillation. The cooled solution was made strongly acid to pH-paper with 1:1 sulfuric acid-water solution and extracted with three 100 ml. portions of ether. The combined ether extracts were extracted with two small portions of saturated salt solution and filtered through anhydrous magnesium sulfate. The ether was removed by distillation and the viscous liquid residue was transferred to a 125 ml. Claisen flask, the side arm of which was packed with glass helices. The last traces of ether and that used in the transfer were removed under reduced pressure. The flask was then placed in an oil bath and the temperature of the mixture slowly raised to 180°. Vigorous bubbling of the liquid began at 180° C. and continued as the temperature was raised to 195°. The temperature of the liquid was maintained at this level until bubbling of the liquid ceased. The cooled flask was then equipped with a capillary tube and attached to a multiple receiver. The liquid was distilled at reduced pressure and the portion collected boiling at 136-138°/23 mm. The yield of ethyl-(1-methylbutyl) acetic acid was 20.2 g. or 49% based on diethyl ethylmalonate.

A sample of the material was dissolved in methanol and titrated with standard sodium hydroxide using phenolphthalein indicator. The material was found to be 99.1% pure based on the molecular weight of ethyl-(1-methylbutyl) acetic acid.

An infrared spectra of a 1% w/v solution of the acid was deter-
mined on a Perkin-Elmer Infracord. The compound exhibited a strong carbonyl peak at 5.9 μ. All of the acetic acids synthesized displayed a band in this region. In addition, the allyl derivatives had a carbon-carbon double bond peak at 6.2 μ.

The substituted acetic acids synthesized in this study are listed in Table 6. Allylisopropyl acetic acid was found to be 97.1% pure by titration. The liquid was redistilled but the purity was not improved.

III Determination of the Rate Constants for the Acid Catalyzed Esterification of the Substituted Acetic Acids in Methanol at 30°

The rates of hydrogen chloride catalyzed esterification of the substituted acetic acids in methanol were determined by the method of Smith. Anhydrous methanol was prepared by distillation of commercial "absolute" methanol through a 1 x 30 inch electrically heated column packed with glass helices. A solution of hydrogen chloride in methanol was prepared by passing tank hydrogen chloride through a tower packed with calcium chloride and then through one containing glass wool and finally through the methanol contained in a flask protected from atmospheric moisture. The concentration of the hydrogen chloride was determined by titration with standard sodium hydroxide using α-naphtholbenzine as indicator. The solution was adjusted to approximately 0.005 N with dry methanol and the exact concentration determined by titration with standard base. The concentration of the solution was found to be

### Table 6. Synthesis of Substituted Acetic Acids

<table>
<thead>
<tr>
<th>Acetic Acid</th>
<th>Malonate</th>
<th>Halide</th>
<th>Boiling Range (°C/mm.)</th>
<th>Yield (%)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylisoamyl</td>
<td>Ethylisoamyl</td>
<td>Ethylisoamyl</td>
<td>134-136/19</td>
<td>81</td>
<td>99.7</td>
</tr>
<tr>
<td>Diallyl</td>
<td>Diallyl</td>
<td>Diallyl</td>
<td>124-26/19</td>
<td>56</td>
<td>100.1</td>
</tr>
<tr>
<td>Ethyl-(1-methylbutyl)</td>
<td>Ethyl</td>
<td>2-Bromopentane</td>
<td>136-138/23</td>
<td>49</td>
<td>99.1</td>
</tr>
<tr>
<td>Ethyl-sec-butyl</td>
<td>Ethyl</td>
<td>sec-Butyl Bromide</td>
<td>114-18/14</td>
<td>40</td>
<td>100.0</td>
</tr>
<tr>
<td>Allylisobutyl</td>
<td>Allyl</td>
<td>Isobutyl Bromide</td>
<td>128-131/21</td>
<td>49</td>
<td>99.5</td>
</tr>
<tr>
<td>Allylisopropyl</td>
<td>Allyl</td>
<td>Isopropyl Bromide</td>
<td>122-30/21</td>
<td>56</td>
<td>97.1</td>
</tr>
<tr>
<td>Ethyl-n-butyl&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Purchased commercially
0.00503 N in hydrogen chloride. A sample of the substituted acetic acid, calculated to yield a final concentration of about 0.5 M when diluted with 25 ml. of the HCl-methanol solution, was weighed in a 50 ml. Erlenmeyer flask. The flask was closed with a neoprene stopper and placed in a constant temperature bath set at 30° ± 0.01°. One hour was allowed for temperature equilibration of the sample and the HCl-methanol solution. Twenty-five ml. of the HCl-methanol solution was pipetted into the flask containing the substituted acetic acid and the zero-time recorded when one-half of the solution had been added. At various intervals 2 ml. aliquots of the solution were removed and titrated with standard sodium hydroxide solution using phenolphthalein indicator. The titration volume was corrected for the hydrogen chloride present in the sample. The rate constants for the esterification were calculated for the expression

\[ k = \frac{2.303 (r + a) \log a/a-x - x}{(HCl)rt} \]

where,  
\( k = \) the pseudo-first-order rate constant  
\( a = \) the original concentration of substituted acetic acid  
\( a - x = \) the concentration of the substituted acetic acid at time \( t \)  
\( x = \) the concentration of ester formed in time \( t \)  
\( (HCl) = \) the concentration of hydrogen chloride catalyst  
\( r = 0.25 \) at 30°

The constant \( r \), in the above equation compensates for the competition between the water formed in the reaction and the methanol solvent for the hydrogen chloride catalyst. A typical example of the results obtained by this procedure is shown in Table 7. Duplicate determinations
were performed on all compounds and excellent agreement was found between per cent reaction and time in all cases. The average rate constants listed in Table 8 were obtained from the rate constants calculated between 30 and 80% reaction except for the slower reacting compounds. The per cent reaction covered by the average rate constants are also listed in Table 8. The extremely slow rate of reaction of the last three compounds listed in the table permitted only a small percentage of the reaction to be covered.

Table 7. The Acid Catalyzed Esterification of Ethylisoamylacetic Acid in Methanol at 30°

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>a-x (Moles/Liter)</th>
<th>( k ) (liter mole(^{-1}) hour(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.76</td>
<td>0.3442</td>
<td>2.89</td>
</tr>
<tr>
<td>52.12</td>
<td>0.3100</td>
<td>2.67</td>
</tr>
<tr>
<td>59.65</td>
<td>0.2961</td>
<td>2.61</td>
</tr>
<tr>
<td>73.78</td>
<td>0.2738</td>
<td>2.51</td>
</tr>
<tr>
<td>97.07</td>
<td>0.2445</td>
<td>2.37</td>
</tr>
<tr>
<td>122.43</td>
<td>0.2158</td>
<td>2.31</td>
</tr>
<tr>
<td>155.90</td>
<td>0.1885</td>
<td>2.20</td>
</tr>
<tr>
<td>193.18</td>
<td>0.1622</td>
<td>2.13</td>
</tr>
<tr>
<td>241.08</td>
<td>0.1384</td>
<td>2.03</td>
</tr>
</tbody>
</table>

Table 8. Rate Constants for the Acid Catalyzed Esterification of Substituted Acetic Acids in Methanol at 30°

<table>
<thead>
<tr>
<th>Acid</th>
<th>( k \times 10^3 ) (liter mole(^{-1})sec(^{-1}))</th>
<th>Percent Reaction Covered by Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic(^a)</td>
<td>81.4 ± 1.0</td>
<td>20-80</td>
</tr>
<tr>
<td>Diallylacetic</td>
<td>1.3 ± 0.1</td>
<td>30-80</td>
</tr>
<tr>
<td>Allylisobutylacetic</td>
<td>0.89 ± 0.08</td>
<td>30-80</td>
</tr>
<tr>
<td>Ethylisoamylacetic</td>
<td>0.80 ± 0.06</td>
<td>30-80</td>
</tr>
<tr>
<td>Ethyl-n-butylacetic</td>
<td>0.75 ± 0.06</td>
<td>30-80</td>
</tr>
<tr>
<td>Allylisopropylacetic</td>
<td>0.16 ± 0.02</td>
<td>20-33</td>
</tr>
<tr>
<td>Ethyl-sec-butylacetic</td>
<td>0.11 ± 0.02</td>
<td>15-25</td>
</tr>
<tr>
<td>Ethyl-(1-methylbutyl) acetic</td>
<td>0.11 ± 0.02</td>
<td>15-22</td>
</tr>
</tbody>
</table>

\(^a\)From data of Smith\(^{23}\)
DISCUSSION

The linear relationship found between log $A_t$ and time indicates a first-order dependency of the rate of decomposition on the concentration of barbiturate. Jackson$^{24}$ reported that the interference of degradation products in the ultraviolet assay of barbital was negligible. On this basis, it was assumed that the spectrophotometric method measured only undegraded barbiturate. The linear dependency of log $A_t$ on time indicates that this was a reasonable assumption.

Correlation of the Rates of Decomposition with the Taft Polar and Steric Substituent Constants

The steric substituent constants for the 5,5-disubstituted barbituric acids were calculated using equation 3 and the rates of acid-catalyzed esterification of the similarly substituted acetic acids. These constants, together with the polar substituent constants, are listed in Table 9. The rate constant for the esterification of ethylisopropylacetic acid was not determined in this investigation and therefore the steric substituent constant for Probarbital (5-ethyl-5-isopropylbarbituric acid) is not available.

Table 9. Polar and Steric Substituent Constants for the 5,5-Disubstituted Barbituric Acid Derivatives

<table>
<thead>
<tr>
<th>5,5-Disubstituted Barbituric Acid</th>
<th>Log $k_{obs}$</th>
<th>$\sigma^+a$</th>
<th>$E_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diallyl (Diallyl Barbituric Acid)</td>
<td>-1.105</td>
<td>-0.120</td>
<td>-1.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\log k_{obs}$</th>
<th>Polar Constant</th>
<th>Steric Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl (Barbital)</td>
<td>-1.658</td>
<td>-0.225</td>
<td>$-1.98^b$</td>
</tr>
<tr>
<td>Ethyl-n-butyl (Butethal)</td>
<td>-1.737</td>
<td>-0.245</td>
<td>$-2.04$</td>
</tr>
<tr>
<td>Ethylisoamyl (Amobarbital)</td>
<td>-1.770</td>
<td>-0.245</td>
<td>$-2.09$</td>
</tr>
<tr>
<td>Phenylethyl (Phenobarbital)</td>
<td>-1.793</td>
<td>0.04</td>
<td>$-1.50^b$</td>
</tr>
<tr>
<td>Allylisobutyl (Allylbarturic Acid)</td>
<td>-2.013</td>
<td>-0.190</td>
<td>$-1.96$</td>
</tr>
<tr>
<td>Allylisopropyl (Aprobarbital)</td>
<td>-2.678</td>
<td>-0.185</td>
<td>$-2.71$</td>
</tr>
<tr>
<td>Ethyl-sec-butyl (Butabarbital)</td>
<td>-3.041</td>
<td>-0.255</td>
<td>$-2.87$</td>
</tr>
<tr>
<td>Ethyl-(1-methylbutyl) (Pentobarbital)</td>
<td>-3.119</td>
<td>-0.255</td>
<td>$-2.87$</td>
</tr>
</tbody>
</table>

aThis parameter refers to the summation of the polar constants of the substituents on the barbituric acid molecule. The values of these constants were taken from the data of Lamb and Harris\(^{25}\).

bFrom the data of Taft\(^{26}\).

The log $k_{obs}$ values of the barbiturates at 75° and the polar and steric substituents constants were fitted to equation 5 by the method of least squares (Appendix II). The reaction constants in this correlation were found to be $\phi = -2.24 \pm 0.09$ and $\delta = 1.523 \pm 0.003$ and


\(^{26}\)Newman, op. cit., p. 6.
the intercept \( \log k_0 = 0.79 \pm 0.01 \). The magnitude of the reaction constants is in reasonable agreement with those of reaction series exhibiting normal ester hydrolysis. However, the sign of the polar reaction constant is the opposite of that expected in a reaction of this type. The negative value implies that the rate of reaction is increased by electron donating groups and retarded by electron withdrawing groups. This result is contrary to that found in normal base-catalyzed ester hydrolysis\(^{27}\). Since base-catalysis was observed in this study it would be expected that electron withdrawing groups would decrease the electron density at the reaction site, facilitate an attack by a base, and thus increase the rate of reaction.

Correlation of \( \log k_{\text{obs}} \) with \( E_s \) alone (Fig. 2) indicates a reasonably good fit of the data to equation 4. The coefficient of determination calculated by the least squares method (Appendix I) is 0.81. This means that 81\% of the variation in \( \log k \) is explained by the steric parameter. On the other hand, the relationship between \( \log k_{\text{obs}} \) and \( S_r^* \) (Fig. 3) leads to a coefficient of determination of only 0.16, i.e., 16\% of the variation in \( \log k_{\text{obs}} \) is explained by the polar effects of the substituents. The multiple correlation of \( \log k_{\text{obs}} \) with steric and polar parameters leads to a coefficient of determination of 0.994 and proposes that 99.4\% of the variation in \( \log k \) is explained by the combined polar and steric effects of the substituents.

and that only 0.6% is due to experimental error.

The polar and steric constants of the barbiturates, as shown in Table 9, vary in a similar manner. Both constants become larger and more negative as the rate constant decreases (log $k_{obs}$ becomes more negative). A linear correlation between these variables, although chemically meaningless, leads to a coefficient of determination equal to 0.42, i.e., 42% of the variation in the polar constant is explained by the steric constant. Apparently the polar constant adds little to the correlation found but, because of the correlation between the polar and steric constants, it would appear that the variation in log $k$ is better explained by both substituent constants than either one alone. Thus the negative sign of the polar constant and the correlation obtained from equation 5 is probably due to the coincidental fit of the data and not justifiable from a chemical point of view. The variation in rate of decomposition in the barbiturate series appears then to be a function only of the steric effects of the substituents. The equation which describes this variation is given by

$$\log k_{obs} = 1.242 E_s + 0.620$$

(18)

This equation was used to calculate the line shown in Fig. 3. The value of $\delta$ is in good agreement with that obtained by Taft for the methoxide-catalyzed methanolysis of $l$-menthyl esters ($\delta = +1.301$) and the one for the acid catalyzed methanolysis of $\beta$-naphthyl esters ($\delta = +1.376$). These results then lend support to the assumption that the mechanism of phenobarbital decomposition is similar to the one
Fig. 2. Correlation of log $k_{obs}$ with $E_s$ values.
Fig. 3. Failure of correlation of log $k_{obs}$ with $S\sigma^*$ values.
established for ester hydrolysis. Furthermore, the existence of the relation described by equation 18 indicates that this mechanism is consistent in the barbiturate series.

Effect of Buffer Concentration on Rate of Decomposition of Barbital and Diallyl Barbituric Acid at 75°

The results listed in Table 5 indicate that rate of decomposition of diethyl barbituric acid (barbital) is not dependent on the concentration of the buffer. Diallyl barbituric acid (dial), on the other hand, shows a slight but experimentally discernible increase in rate with increasing buffer concentration indicating interaction with a buffer component. The buffer component responsible for the increase in rate is assumed to be the ethanolamine base. A plot of $k_{obs}$ versus $(E)$, as shown in Fig. 4, is linear within the experimental error of the rate constants indicating a first-order dependency of the rate of decomposition of dial on the concentration of ethanolamine base. The value of $k_g$, the specific rate constant for ethanolamine base, was calculated by the least squares method to be $2.4 \pm 0.1 \times 10^{-2}$ liter mole$^{-1}$ hr.$^{-1}$.

Effect of Hydroxide Ion Concentration on the Rate of Decomposition of Barbital and Diallyl Barbituric Acid at 75°

A linear relationship between $k_{obs}$ and (OH) is not observed in regions of low hydroxide ion concentrations due to the presence of appreciable amounts of the undissociated acid (Figures 5 and 6). The observed rate constants were corrected for the presence of undissociated
Fig. 4. A plot showing the first-order dependency of the decomposition of dial on the ethanolamine base concentration.
acid by dividing them by the degree of dissociation of the compound at the experimental temperature and hydroxide concentration. The values of barbital and dial were calculated using the Ka values obtained from the pKa values of these compounds at 75°. The pKa of barbital at 75° was calculated from the equation of Manov and co-workers for the pKa from 0 to 60° and is given by

$$pKa = 2324.47/T + 0.0118562 T - 3.3491$$

From this expression the pKa at 75° was found to be 7.36 and at 25° it is 7.97. The pKa for dial at 25° is 7.79 as listed by Krahl. The effect of temperature on the pKa of dial was assumed to be similar to that for barbital and the same correction (-0.61) was applied to the pKa at 25° giving a value of 7.18 at 75°. The corrected rate constants for barbital at the various hydroxide ion concentrations are listed in Table 10.

<table>
<thead>
<tr>
<th>(OH) x 10⁴ (Moles/Liter)</th>
<th>kobs/α (Hr.⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.22</td>
<td>2.06</td>
</tr>
<tr>
<td>0.47</td>
<td>2.09</td>
</tr>
<tr>
<td>0.87</td>
<td>2.09</td>
</tr>
<tr>
<td>2.1</td>
<td>2.23</td>
</tr>
<tr>
<td>4.9</td>
<td>2.44</td>
</tr>
</tbody>
</table>


Fig. 5. A plot showing the non-linear relationship between $k_{obs}$ and hydroxide ion concentration for barbital.
Fig. 6. A plot showing the non-linear relationship between $k_{\text{obs}}$ and hydroxide ion concentration for dial.
A plot of the corrected rate constants, $k_{obs}/\alpha$ versus (OH) (Fig. 7) is linear and indicates a first-order dependency of the reaction on hydroxide ion concentration. The specific catalytic constant, $k_{OH}$ calculated from the least squares line is $8.2 \pm 0.04$ liter mole$^{-1}$ hr.$^{-1}$ and the intercept, $k_0$ is $2.04 \times 10^{-2}$ hr.$^{-1}$.

The observed rate constants of dial were corrected for the presence of undissociated acid. In addition, they were corrected for the effect of the different concentrations of ethanolamine present at each hydroxide ion concentration by subtracting the factor $k_E(E)$ from each value. The corrected rate constants are listed in Table II.

Table II. Rate Constants for the Decomposition of Dial Anion at Various Hydroxide Ion Concentrations Corrected for the Interaction with Ethanolamine Base

<table>
<thead>
<tr>
<th>(OH) x $10^4$ (Moles/Liter)</th>
<th>$k_{obs}/\alpha$ (Hr.$^{-1}$)</th>
<th>$k_{obs}/\alpha - k_E(E)$ (Hr.$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21</td>
<td>6.21</td>
<td>6.10</td>
</tr>
<tr>
<td>0.45</td>
<td>6.53</td>
<td>6.34</td>
</tr>
<tr>
<td>0.66</td>
<td>6.80</td>
<td>6.53</td>
</tr>
<tr>
<td>2.1</td>
<td>8.02</td>
<td>7.67</td>
</tr>
<tr>
<td>4.8</td>
<td>10.27</td>
<td>9.85</td>
</tr>
</tbody>
</table>

A plot of these corrected values against (OH) is linear indicating a first-order dependency on hydroxide ion concentration (Fig. 8). This result also corroborates the assumption that ethanolamine base is the buffer component responsible for the increase in rate. The specific catalytic constant, $k_{OH}$ obtained from the least squares line is $81.0 \pm 0.8$ liter mole$^{-1}$ hr.$^{-1}$ and the intercept, $k_0$ is $5.96 \times 10^{-2}$ hr.$^{-1}$. 
Thus, for barbital

\[ k_{\text{obs}} = \alpha \sqrt{2.04 \times 10^{-2} + 8.2 \pm 0.4 \, \text{(OH)}}, \]

and for dial

\[ k_{\text{obs}} = \alpha \sqrt{5.96 \times 10^{-2} + 81.0 \pm 0.8 \, \text{(OH)} + 2.4 \pm 0.1 \times 10^{-2} \, \text{(E)}}. \]

The contribution by ethanolamine base to the decomposition of dial anion, although small, is experimentally perceptible. It would appear from the results obtained that the mechanism of barbital decomposition is different from that of dial since only catalysis by the hydroxide ion is recognized for barbital. However, considering the difference in magnitude of \( k_{\text{OH}} \) for the two compounds, a proportionate difference in \( k_\text{E} \) would lead to a value for barbital which would not be experimentally detectable with the method employed. There is then a good possibility that the mechanism of reaction of these two compounds is the same but the low reactivity of ethanolamine precludes observation of a kinetic term for its catalytic effect in the decomposition of barbital anion.

The steric energy relationship obtained, although not a strong correlation, lends support to the postulation of a single mechanism for the entire series of barbiturates studied.

**Pharmaceutical Significance of the Results**

Equation 18 can be used to predict the rate of reaction of any 5,5-disubstituted barbituric acid under the same conditions provided the steric constant for the desired compound are available. The constants in this equation are, however, temperature dependent. The
Fig. 7. A plot showing the first-order dependency of the decomposition of barbital anion on the hydroxide ion concentration.
Fig. 8. A plot showing the first-order dependency of the decomposition of dial anion on the hydroxide ion concentration.
steric substituent constants on the other hand are independent of
temperature. These may be used to establish and log $k_0$ values at
any temperature where rate constants for two or more barbituric acid
derivatives are available. Relationships of this type would be valuable
in choosing the most stable compound to use in a pharmaceutical formu-
lation and predicting the shelf-life of the product.

The fact that the decomposition of barbituric acid derivatives
are dependent only on the concentration of the anionic species has
particular significance in product development. It would be necessary
for maximum stability to adjust the pH of a solution of the compound
to a region (pH~6) where the barbiturate is in its undissociated form.
Problems of solubility are involved, however, and a balance between
maximum stability and solubilization would have to be considered.

The effect of ethanolamine on the decomposition of diallyl
barbituric acid typifies another problem which may be encountered in
product development. It would be expected that other amine compounds
such as ephedrine would have a similar effect on the stability of a
barbiturate if formulated in combination. Since it was shown that the
rate of decomposition was accelerated only by the amine base, it would
be necessary for maximum stability to adjust the pH to a region where
the concentration of the free amine is negligible.
SUMMARY AND CONCLUSIONS

1. The rates of base-catalyzed decomposition of a series of 5,5-disubstituted barbituric acid derivatives were determined in an ethanolamine buffer solution at 60° and pH 9.19 and at 75° and pH 9.03. A first-order dependency on barbiturate concentration was noted in all instances.

2. A series of substituted acetic acids were synthesized having substituents similar to the barbituric acids studied. The rate constants for the acid-catalyzed esterification of the substituted acetic acids in methanol at 30° were determined. The Taft steric constants for the substituents were calculated from these rate constants.

3. A correlation of the logarithms of the rate constants for the decomposition of the 5,5-substituted barbituric acids at 75° with the Taft polar and steric constants of the substituents resulted in a coincidental fit of the data to an equation with two adjustable parameters. However, a reasonable correlation of the rates with the steric parameters was found. The value of the reaction constant obtained suggested a normal ester hydrolysis mechanism when compared with a reaction constant for a series known to have this mechanism.

4. The rates of decomposition of barbital and diallyl barbituric acid were determined at various hydroxide ion and buffer concentrations. The rates of reaction of both compounds were found to be first-order with respect to the concentration of the barbituric anion and first-order with respect to hydroxide ion concentration. The rate of decomposition of diallyl barbituric acid was also found to be first-order.
with respect to ethanolamine base concentration. The mechanism of reaction of the two compounds is considered to be the same even though the rate of barbital decomposition was apparently not influenced by the buffer concentration.

5. The steric energy relationship obtained supports the postulation of a single mechanism which is consistent for the decomposition of barbital and dial as well as other barbituric acid derivatives.

The following conclusions can then be stated:

1. The rates of base-catalyzed decomposition of the 5,5-disubstituted barbituric acid derivatives quantitatively parallel the Taft steric constants of the substituents.

2. The steric reaction constant obtained suggests a mechanism for the decomposition of barbituric acid derivatives which is similar to the one proposed for ester hydrolysis.

3. The mechanism of decomposition is consistent in the compounds studied.
APPENDIX I

Linear Correlation of Two Variables. The Method of Least Squares

The estimating equation for the line is given by

$$Y = a + bX$$

where $b$ is the slope of the line and $a$ is the intercept. These parameters can be evaluated from the following equations.

$$S_{x^2} = S_{X^2} - (S_X)/N$$
$$S_{xy} = S_{XY} - (S_{XY})/N$$
$$S_{y^2} = S_{Y^2} - (S_Y)^2/N$$

where $S$ represents a summation sign and $N$ is the number of observations.

Then

$$b = \frac{S_{xy}}{S_{x^2}}$$

and

$$a = \bar{y} - b\bar{x}$$

where $\bar{y}$ and $\bar{x}$ are the average $Y$-values and $X$-values respectively. The standard deviation of the correlation is given by

$$s_d = \frac{S_{y^2} - (S_{xy})^2/S_x^2}{N - 2}$$

and the standard deviation of the slope is given by

$$s_b = \frac{S}{(S_{x^2})^{1/2}}$$

The coefficient of determination for the correlation is evaluated from the expression

$$r = (S_{xy})^2/(S_x^2)(S_y^2)$$


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APPENDIX II

Multiple Correlation by the Method of Least Squares

The estimating equation for a correlation of three variables is

\[ Y = b_1 X_1 + b_2 X_2 + b_0 \]

The coefficients of the variables are evaluated from the following equations:

\[
C_{11} = \text{NSX}_2^2 - (\text{SX}_2)^2
\]
\[
C_{12} = \text{SX}_1 \text{SX}_2 - \text{NSX}_1 X_2
\]
\[
C_{13} = \text{SX}_1 X_2 \text{SX}_2 - \text{SX}_1 \text{SX}_2^2
\]
\[
C_{22} = \text{NSX}_1^2 - (\text{SX}_1)^2
\]
\[
C_{23} = \text{SX}_1 \text{SX}_1 X_2 - \text{SX}_1^2 \text{SX}^2
\]
\[
C_{33} = \text{SX}_1^2 \text{SX}_2^2 - (\text{SX}_1 X_2)^2
\]
\[
D = C_{11} \text{SX}_1^2 + C_{12} \text{SX}_1 X_2 + C_{13} \text{SX}_1
\]
\[
b_1 = \frac{1}{D} (C_{11} \text{SX}_1 Y + C_{12} \text{SX}_2 Y + C_{13} SY)
\]
\[
b_2 = \frac{1}{D} (C_{12} \text{SX}_1 Y + C_{22} \text{SX}_2 Y + C_{23} SY)
\]
\[
b_0 = \frac{1}{D} (C_{13} \text{SX}_1 Y + C_{23} \text{SX}_2 Y + C_{33} SY)
\]

The standard deviation of the correlation is given by

\[
\delta^2 = \frac{\text{SY}^2 - b_1 \text{SX}_1 Y - b_2 \text{SX}_2 Y - b_0 \text{SY}}{N - 3}
\]

and the standard deviations of the coefficients are

\[
s_{b_1} = (C_{11}/D) \delta^2
\]
\[
s_{b_2} = (C_{22}/D) \delta^2
\]
\[
s_{b_0} = (C_{33}/D) \delta^2
\]

31Pavelich and Taft, op. cit., p. 8.
The multiple coefficient of determination is given by the expression

\[ R^2 = \frac{b_1 S_{X_1} Y - b_2 S_{X_2} Y - b_0 S_Y - (S_Y)^2}{S_Y^2 - (S_Y)^2/N} \]

In using the above equations to solve the equation

\[ \log k_{obs} = \rho^* S\sigma^* - \delta E_s - \log k_0 \]

the following definitions are made

- \( Y = \log k_{obs} \)
- \( b_0 = \log k_0 \)
- \( b_1 = \rho^* \)
- \( b_2 = \delta \)
I, Donald Joseph Lamb, was born in Pittsburgh, Pennsylvania, October 29, 1931. I received my undergraduate training at The Ohio State University, which granted me the Bachelor of Science degree in Pharmacy in 1954. I received a Master of Science degree in Pharmacy from the same university in 1955. I held a research position in the Physiological Chemistry Branch of the Medical Research Directorate, Army Chemical Center, Maryland, while on active duty with the United States Army from 1955 to 1957. I was awarded the E. Mead Johnson Memorial Fellowship by the American Foundation for Pharmaceutical Education in September, 1958. I held this fellowship for two years while completing the degree Doctor of Philosophy.