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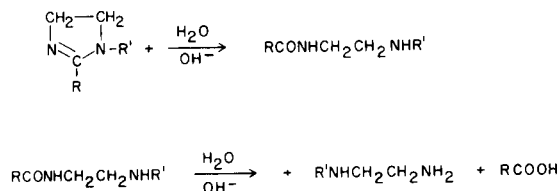
## The Influence of Alkyl Substituents on the Rates of Hydrolysis of 2-Imidazolines

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A number of 2-imidazolines have been hydrolyzed in basic 95% ethanol, and the activation energies and half-lives of these reactions have been determined. The reactions are base catalyzed and lead to the formation of amides through fission of the ring between positions one and two. The reaction rates are strongly influenced by various ring substituents.

A number of workers have reported the opening of the 2-imidazoline ring under various hydrolytic conditions, (2-9), but the minimum conditions for hydrolysis and the influence of ring substituents have not received attention up to now. Furthermore, no kinetic data have been made available from previous studies.

The course of the reaction may be formulated as follows:



We have found the above reaction sequence occurs in the base catalyzed hydrolysis of 2-substituted-1-hydroxyethyl-2-imidazolines and 1-substituted-2-pentyl-2-imidazolines. Miescher, *et al.*, (8) and Zienty (9) have reported similar reactions in the acid catalyzed hydrolysis of 1-acylated-2-substituted-2-imidazolines. Miescher found that 1-unsubstituted imidazolines were resistant to acid catalyzed hydrolysis. Our work indicates that the hydrolysis of 1,2-dialkyl-2-imidazolines is catalyzed by bases and inhibited by acids.

### KINETIC STUDIES

Two series of kinetic studies were carried out to determine the effects of various substituents in the one and two positions of 2-imidazolines. In one series the group in the 1-position was held constant while the 2-substituent was varied. In the second series this procedure was reversed.

The hydrolytic reactions were run in 95% ethanol which was  $3.75 \times 10^{-2}$  molar with respect to sodium hydroxide. There was evidence that the reaction rate reached a maximum as base concentration was increased and the particular concentration used was selected because it was in the range of the maximum rates.

The reactions were followed spectrophotometrically by observing the disappearance of the  $-\text{C}=\text{N}-$  absorption peak at  $230 \text{ m}\mu$ . Reaction conditions were such that *pseudo* first order kinetics were observed, and all half-lives and rate constants were determined graphically. Tables I and II summarize the results of these experiments.

Similar experiments show that the hydrolysis of 2-imidazolines in acidic solutions is very slow or non-existent. An experiment wherein 2-heptadecyl-1-hydroxyethyl-2-imidazoline was hydrolyzed in acidic 95% ethanol gave a half-life of 13,680 minutes at  $70^\circ$ . A series of experiments in buffered aqueous solutions below  $\text{pH } 7$  showed no hydrolysis of 1-hydroxyethyl-2-pentyl-2-imidazoline after 6,780 minutes at  $25^\circ$ .

### DISCUSSION

The imidazolines are weak monoacid bases. It is reasonable to assume that in aqueous solution they are normally hydrogen bonded to water molecules and that an equilibrium exists between the ionized and unionized forms.

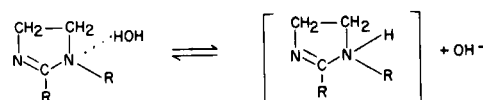
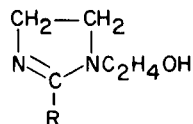


TABLE I

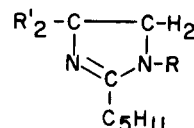
The Effect of 2-Substituents on Half-lives and Activation Energies of 1-Hydroxyethyl-2-imidazolines



R	T <sup>1</sup> / <sub>2</sub> at 70.48°C Minutes	T <sup>1</sup> / <sub>2</sub> at 58.26°C Minutes	T <sup>1</sup> / <sub>2</sub> at 48.90°C Minutes	E activation cal./g. mole
H-	3.0 2.7	6.5 6.2	14.6 14.25	16960 ± 2780
CH <sub>3</sub> -	28.5 28.5	70.5 69	153 148	16990 ± 1770
C <sub>2</sub> H <sub>5</sub> -	17.5 18	40.2 38	81 80	15770 ± 2190
CH(CH <sub>3</sub> ) <sub>2</sub> -	46 44	96 92	194 180	14560 ± 2660
C(CH <sub>3</sub> ) <sub>3</sub> -	95 97	264 258	612 612	18980 ± 1580
C <sub>5</sub> H <sub>11</sub> -	25 25	57.5 55	119 117	15880 ± 2670
C <sub>17</sub> H <sub>35</sub> -	24 24	56 52	115 114	15360 ± 3060

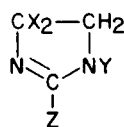
TABLE II

The Effect of Various Substituents on Half-lives and Activation Energies of 2-Pentyl-2-imidazolines



R	R'	T <sup>1</sup> / <sub>2</sub> at 70.48°C Minutes	T <sup>1</sup> / <sub>2</sub> at 58.26°C Minutes	T <sup>1</sup> / <sub>2</sub> at 48.90°C Minutes	E activation
H	H	287 288	738 732	1692 1698	18160 ± 1860
CH <sub>3</sub>	H	32 32	66.5 66	131 132	14460 ± 1980
C <sub>2</sub> H <sub>5</sub>	H	59 58	121.5 120	236 236	14270 ± 1960
C <sub>2</sub> H <sub>4</sub> OH	H	25 25	57.5 55	119 117	15880 ± 2667
C <sub>2</sub> H <sub>4</sub> OC <sub>2</sub> H <sub>5</sub>	H	65 62.7	137 137	267 270	14700 ± 1800
CH(CH <sub>3</sub> ) <sub>2</sub>	H	450 453	1020 1044	1878 1884	14650 ± 2050
CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	65 days approximately.			

TABLE III



X	Y	Z	Boiling Point and Pressure	Ultraviolet Absorption, Ethanol		Analysis			
						Neutral Eq.		Nitrogen	
				Calcd.	Found	Calcd.	Found		
H	C <sub>2</sub> H <sub>4</sub> OH	C <sub>5</sub> H <sub>11</sub>	156°/.07 mm	231	5320	184	182	15.21	15.21
H	C <sub>2</sub> H <sub>4</sub> OH	H	m. p. 62-63°	234	6670	114	114	24.55	24.28
H	C <sub>2</sub> H <sub>4</sub> OH	CH <sub>3</sub>	m. p. 49-53°	231	6160	128	129	21.85	21.49
H	C <sub>2</sub> H <sub>4</sub> OH	C <sub>2</sub> H <sub>5</sub>	121-122°/.07 mm	231	5600	142	141	19.70	19.64
H	C <sub>2</sub> H <sub>4</sub> OH	<i>iso</i> -C <sub>3</sub> H <sub>8</sub>	125-126°/.2 mm	231	5710	156	153	17.93	17.86
H	C <sub>2</sub> H <sub>4</sub> OH	-C(CH <sub>3</sub> ) <sub>3</sub> (a)	180-190°/25 mm	232	5130	170	174	16.45	16.07
H	H	C <sub>5</sub> H <sub>11</sub>	m. p. 53-54°	221	4410	140	138	19.98	19.90
H	CH <sub>3</sub>	C <sub>5</sub> H <sub>11</sub>	50-52°/.15 mm	230	5650	154	150	18.18	18.00
H	C <sub>2</sub> H <sub>5</sub>	C <sub>5</sub> H <sub>11</sub>	68-70°/.07 mm	232	5920	168	167	16.65	16.57
H	CH(CH <sub>3</sub> ) <sub>2</sub>	C <sub>5</sub> H <sub>11</sub>	79-80°/.15 mm	231	5560	182	187	15.37	15.38
CH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	C <sub>5</sub> H <sub>11</sub>	228-230°/630 mm	230	6540	210	207	13.25	13.28

(a) I. R. spectrum shows the presence of amide. Low yields made purification difficult.

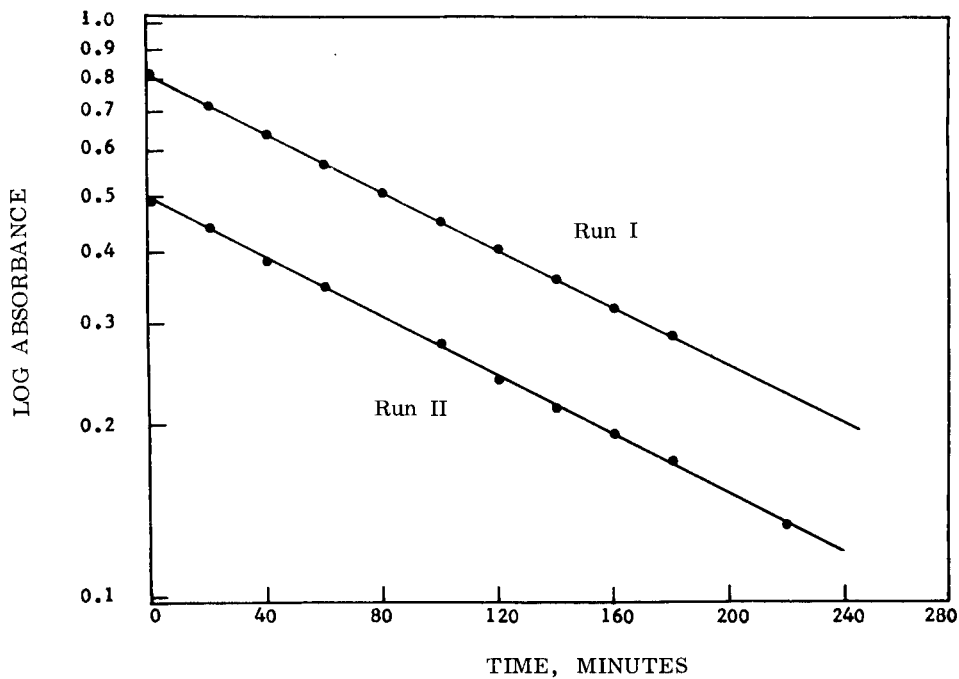


Figure 1. Semi-logarithmic plot of absorbance against time for the hydrolysis of 1-hydroxyethyl-2-pentyl-2-imidazoline at 48.9°.

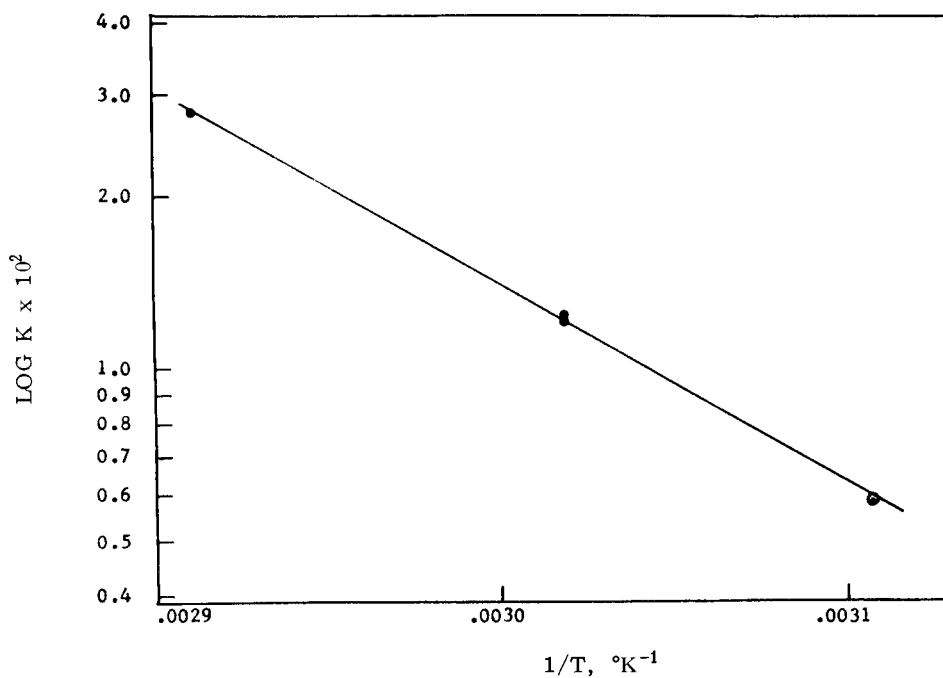
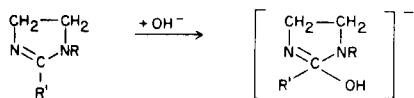


Figure 2. Temperature dependence of the rate constants for the hydrolysis of 1-hydroxyethyl-2-pentyl-2-imidazoline.

In view of the resistance to acid hydrolysis, it seems that the salt of the imidazoline takes little, if any, part in hydrolysis.

The structure of the amides resulting from hydrolysis, and the fact that hydrolysis is catalyzed by hydroxide ion, suggest that there is an initial attack by hydroxide on the number two carbon of the ring.



The number two carbon in the imidazoline ring should be slightly positive. Any substituent that reduces this positive charge should also reduce the probability of attack by hydroxide ion; and this should lead to a slower reaction. This effect should be observed regardless of the position of the substituent.

The electron donating ability of alkyl groups is in the order  $-\text{C}(\text{CH}_3)_3 > -\text{CH}(\text{CH}_3)_2 > -\text{C}_5\text{H}_{11} > -\text{C}_2\text{H}_5 > -\text{CH}_3 > -\text{H}$ ; and it would be expected that the half-lives for the hydrolysis of compounds with these substituents would be in the same order. Comparison of this postulate with Tables I and II shows that the expected order was found in most cases. It is unfortunate that steric hindrance should affect the rate of reaction in the same way as would inductive effects, but at least there is no evidence that the two effects are opposed.

The compounds that do not fall in their expected places are 2-methyl-1-hydroxyethyl-2-imidazoline and 2-pentyl-2-imidazoline. At this time, there is no really satisfactory theory for the unexpected stability of the 2-methyl substituted compound, but a plausible explanation is possible for the other. The low reactivity of 2-pentyl-2-imidazoline may be explained by the fact that the number one nitrogen in this compound is a secondary amine. This increased basicity should lead to decreased reactivity by decreasing the concentration of unionized imidazoline available for reaction.

The extreme stability of 4,4-dimethyl-1-isopropyl-2-pentyl-2-imidazoline is surprising but not inexplicable. This compound should be subject to the inductive effects of a tertiary alkyl group acting through an easily polarizable double bond in addition to possible steric hindrance.

There are several other interesting facts in Table II. The half-lives of 1-ethyl-2-pentyl-2-imidazoline and 1-ethoxyethyl-2-pentyl-2-imidazoline are almost the same. It would be expected that the inductive effects of these two substituents would be about the same order of magnitude; so it seems that steric hindrance by straight chain substituents in the 1-position does not greatly affect the rate of hydrolysis.

The half-life of 1-isopropyl-2-pentyl-2-imidazoline is greater than might be expected on the grounds of inductive effects. It is therefore suggested that

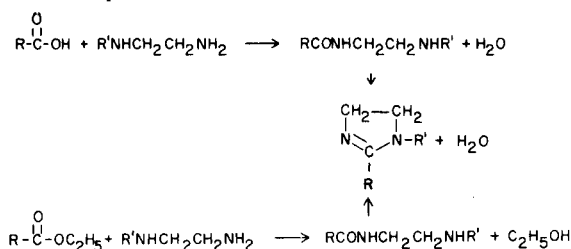
considerable steric hindrance occurs when the 1-substituent is a branched chain alkyl group.

Finally, the half-life of 1-hydroxyethyl-2-pentyl-2-imidazoline seems to indicate that the hydroxyethyl group is a less effective electron donor than a methyl group, and it is probable that this is so. Atomic models, however, show that the hydroxyl group may be in an excellent position to attack the number two carbon of the ring, and there is evidence for this type of attack in other compounds (10).

In summary, the available data do seem to support the postulated attack of hydroxide ion at the number two ring carbon as the initial step in hydrolysis. It seems probable that the initial step is followed by a reaction with water at the number one carbon and subsequent rearrangement to an amide. At present our data are not sufficient to support firm arguments for additional steps in the reaction mechanism.

#### EXPERIMENTAL

All of the imidazolines considered in this study were prepared by procedures based on the methods of Riebsomer (11) or of Morrill (12). One molar equivalent of a carboxylic acid or ethyl ester was mixed with one molar equivalent of an appropriate 1,2-diamine and a little benzene. This mixture was heated from 130 to 230° and the benzene and water were distilled through a 4' helix packed column equipped with a decanter still-head filled with benzene. The still-head was arranged so that benzene was returned to the column and water could be removed. Heating was continued until evolution of water became very slow or stopped. When esters were used, the benzene was not added until one molar equivalent of alcohol was collected. Benzene was then added and the heating continued until water no longer distilled out. This sequence of reactions is illustrated below.



Structure and purity of the imidazolines were determined by infrared and ultraviolet absorption spectra, neutral equivalents and Kjeldahl nitrogen determinations. No effort was exerted to secure high yields from these preparations and considerable quantities of material were often sacrificed to acquire high purity.

Since these syntheses are all very similar, only two examples are given. The properties of the other compounds are given in Table III. All starting materials except some of the diamines were commercially available. The required diamines were synthesized by known procedures (13) or as given in the example.

#### 1-Hydroxyethyl-2-heptadecyl-2-imidazoline.

Forty-eight g. (0.15 mole) of ethyl stearate and 17.2 g. (0.165 mole) of hydroxyethylethylenediamine were heated together at 130 to 230° until approximately 0.15 mole of ethanol was collected. Benzene was then cautiously added and the heating continued until no more water was evolved. The cooled reaction mass was dissolved in boiling petroleum ether (60-90°) and the less soluble amide was removed by repeated fractional crystallization and filtration. The fourth crystallization yielded the crude imidazoline, m.p. 70-75°, which was recrystallized from benzene and repeatedly subjected to evaporative distillation to give the pure white imidazoline, m.p. 70-71°.

U. V.  $\lambda$  max (ethanol) 232 m $\mu$  ( $\epsilon$ , 6,080).

Anal. Calcd. for  $\text{C}_{22}\text{H}_{44}\text{N}_2\text{O}$ : N. E., 352.6; C, 74.93; H, 12.58; N, 7.95. Found: N. E., 352.2; C, 74.96; H, 12.45; N, 7.96.

The first three crops of crystals were combined and recrystallized from ethanol to give 1.2 g. of N-stearoyl-N'-(2-Hydroxyethyl) ethylenediamine, m.p. 108-109°.

Anal. Calcd. for  $\text{C}_{22}\text{H}_{46}\text{N}_2\text{O}_2$ : N. E., 370.6; N, 7.57. Found: N. E., 370; N, 7.42.

Van Slyke amino nitrogen was 0.1%. This establishes the structure indicated. As a further confirmation of structure, the amide was treated with nitrous acid to form the N-nitroso compound.

*Anal.* Calcd. for  $C_{22}H_{45}N_3O_3$ ; N, 10.5. Found: N, 10.13.

#### 1-(2-Ethoxyethyl)-2-pentyl-2-imidazoline.

N-2-Ethoxyethylethylenediamine was prepared by slowly adding 150 g. (1 mole) of ethoxyethyl bromide to 360 g. (6 moles) of refluxing ethylenediamine. The resulting mixture was then treated with saturated KOH solution. The organic layer was separated and distilled to yield 69 g., 52% of the substituted diamine, b.p. 189°, molecular weight 132, N.E., 132.

A solution of 23 g. (0.2 mole) of caproic acid and 26 g. (0.2 mole) of N-2-ethoxyethylethylenediamine in benzene was heated to 230° over a period of several hours. The cooled reaction mass was treated with sodium hydroxide solution. The organic phase was separated, and distillation yielded the pure imidazoline, a faintly yellow oil, b.p. 260-263°.

U. V.  $\lambda$  max (ethanol) 231  $\mu$  ( $\epsilon$ , 6,260).

*Anal.* Calcd. for  $C_{12}H_{24}N_2O$ : N.E., 212; C, 67.87; H, 11.39; N, 13.2. Found: N.E., 210; C, 67.89; H, 11.61; N, 13.2.

#### Absorption Spectra.

The infrared spectra of all the compounds synthesized in this work were recorded as a proof of structure and purity. The carbon to nitrogen double bond shows a strong absorption peak between 6.2 and 6.3  $\mu$  while the amide group absorbs between 6.0 and 6.1  $\mu$ .

The ultraviolet absorption spectra of pure 1,2-dialkyl substituted imidazolines show a single maximum at about 230  $\mu$  while the amides resulting from hydrolysis have an absorption maximum at about 205  $\mu$ .

#### Hydrolysis Products.

N-Steroyl-N'-hydroxyethylethylenediamine was isolated in both alcoholic and aqueous hydrolysis of 1-hydroxyethyl-2-heptadecyl-2-imidazoline. The compound isolated from the hydrolysis reactions had the same melting point, mixed melting point, and infrared spectrum as the amide found in the preparation of the imidazoline.

N-Pentanoyl-N'-hydroxyethylethylenediamine, m.p. 71-72°, was isolated from a simple aqueous solution of 1-hydroxyethyl-2-pentyl-2-imidazoline after the solution was stored several days at room temperature.

*Anal.* Calcd. for  $C_5H_{11}CONHCH_2CH_2NHC_2H_4OH$ : N.E., 202; N, 13.84; primary amino nitrogen, 0. Found: N.E., 203; N, 13.73; primary amino nitrogen, less than 0.2%.

A number of initial hydrolysis reactions were followed by use of an infrared spectrophotometer. The spectra clearly show the build-up of an amide absorption peak at 6.1  $\mu$  as well as the decrease in the -C=N- peak at about 6.3  $\mu$ .

#### Kinetic Studies.

Most of the methods used in following these reactions were based on observing the disappearance of the -C=N- ultraviolet absorption band at an appropriate wave length. Several experiments indicated that Beer's Law was valid for these compounds.

All of the reactions used to determine the effects of ring substituents were run in 95% ethanol that was  $3.75 \times 10^{-2}$  molar with respect to sodium hydroxide. The initial concentration of imidazoline was usually about  $10^{-3}$  molar, but a tenfold change in concentration did not effect the reaction rate constant. Temperature was controlled to one-tenth of a degree and the reaction vessels were found to be free of evaporation losses over a 24 hour period at 70°C. All half-lives were obtained graphically from plots of the logarithm of absorbance against

time.

The usual experimental procedure was to add approximately 750 ml. of basic ethanol solution to a one liter three-necked flask fitted with a condenser, mercury sealed stirrer, and a port for the insertion of a pipet. The condenser was plugged with glass wool to minimize diffusion. The entire bulb of the flask was immersed in a constant temperature bath, and the ethanol solution was stirred until temperature equilibrium was achieved. Ten ml. of the hot solution was then transferred to a 100 ml. volumetric flask and acidified with concentrated hydrochloric acid. The acidified solution was diluted to 100 ml. and mixed for use as a reference solution.

An appropriate quantity of imidazoline was then added to the reaction flask and a few minutes were allowed for mixing. At known time intervals 10 ml. samples were withdrawn and transferred to a 100 ml. volumetric flask partially filled with cool 95% ethanol containing the same quantity of hydrochloric acid as was used in the reference. The volumetric flask was filled to the mark with 95% ethanol containing the same quantity of hydrochloric acid as was used in the reference. The volumetric flask was filled to the mark with 95% ethanol and the contents were mixed. The absorbance of this solution was then determined at about 230 millimicrons with a Beckman D. U. spectrophotometer. Matched quartz cells with ground glass stoppers were used to minimize evaporation loss.

These reactions were normally run through about two half-lives, but the build-up of reaction products sometimes caused a deviation from first-order kinetics after about one half-life.

Figures 1 and 2 show typical plots of the logarithm of absorbance against time and logarithm of the rate constant against  $1/T$  for the hydrolysis of 1-hydroxyethyl-2-pentyl-2-imidazoline in ethanol.

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