The Effect of Structural Variation on the Hydrolysis of Δ^2-Thiazolines

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The hydrolysis of 13 Δ^2-thiazolines has been investigated in the pH range 0–6 at 30°. Analysis of the characteristic, bell-shaped rate–pH profiles as well as the effect of variation in the polar nature of aryl substituents in the 2-position of the thiazoline nucleus support the general validity of a previously proposed mechanism for thiazoline hydrolysis. The rate of hydration of thiazolines has been found to vary by a factor of 38,000 over the series of compounds examined. For ten 2-arylthiazolines, with or without 4-substitution, a linear relationship between the logarithm of the hydrolysis rate constant and the pK of the thiazolinium ion has been noted. A parallel relationship appears valid for 2-methylthiazolines, which are about 250 times more reactive than 2-arylthiazolines of the same pK. The observation of a constant rate of hydrolysis of 2-methylthiazoline at alkaline pH (78°) is discussed.

From time to time, the hypothesis that labile covalent structures are formed in peptides and proteins by interaction of amino acid side chains with each other or with peptide bonds has received attention. The Δ^2-thiazoline system, arising from covalent interaction of the sulfhydryl group of cysteine with an adjacent peptide function, has been the focus of particular interest. Its formation was suggested to explain the "masking" of protein sulfhydryl groups[1]; convincing evidence has been adduced in favor of its presence in the antibiotic polypeptide bacitracin A.[2] A thiazoline ring may also exist in the antibiotic thiostrepton, which is "at least partially of a peptide nature,"[3a] but for which no complete structure has yet been written.[3] Other substances of natural origin known or believed to embody the Δ^2-thiazoline system are firefly luciferin,[4] glutathione in strongly acidic solution,[5] and, possibly, a form of Coenzyme A.[6] The Δ^2-oxazoline grouping, derived analogously from serine, occurs in the antibiotic peptide mycobactin[7]; the suggestion has been made that the unusual serine residue of certain hydrolytic enzymes owes its peculiar reactivity to incorporation into oxazoline linkage.[8]

Interest in the chemical reactivity of Δ^2-thiazolines in aqueous solution has led us to examine the effect of systematic structural variation upon the rate and mechanism of hydrolysis of thiazolines derived from cysteamine and L-cysteine. In recent years, several studies of the hydrolysis of 2-alkylthiazolines have appeared.[5e,9-11] Our findings, based mainly on an investigation of 2-arylthiazolines, support and extend the conclusions reached earlier, notably in the careful studies of Martin and co-workers.[5e,9]

Results

Eleven of the thirteen Δ^2-thiazolines (Figure 1) examined in the course of this work exhibit a characteristic bell-shaped dependence of observed first-order rate constant (k_{obsd}) for initial rate of thiazoline hydrolysis upon pH. This behavior, described by Martin[5e,9] for 2-alkylthiazolines, is thus also shown by 2-arylthiazolines (except for compounds **1** and **2**, to be discussed later) and is illustrated for four substances in Figure 2. Both the position of the maximum of the pH–rate profile and the breadth of the symmetrical bell-shaped curve (as measured by the pH interval separating the two inflection points) vary appreciably with the nature of the substituents on the thiazoline nucleus.

The observed first-order rate constants for the hydrolysis of the parent, unsubstituted, Δ^2-thiazoline **11** and two of its alkyl derivatives **12** and **13** are shown in Figure 2. The rate–pH profile for a representative 2-arylthiazoline (**10**) is seen in Figure 2B. Similar data (not shown) were obtained for seven 2-arylthiazolines with or without 4-substituents (compounds **3–9**). The rate data for the nitrophenylthiazolines **1** and **2** are presented in Figure 3.

Analysis of the kinetic data was based on the assumption of a hydrolytic mechanism identical with that advanced by Martin for 2-methylthiazoline.[5e] It is proposed that thiazoline hydrolysis proceeds *via* attack of water upon the thiazolinium ion to yield an uncharged 2-hydroxythiazolidine intermediate which is converted to a mixture of N- and S-acylcysteamines[5e,10] (Figure 4). Assumption of a steady state in the tetrahedral intermediate results in eq. 1 for the dependence of k_{obsd} upon pH, where K_1 is the dissociation constant of the thiazolinium ion, and k_1, k_2, k_3, and k_5 are the

(1) (a) K. Linderstrøm-Lang and C. F. Jacobsen, *Compt. Rend. Trav. Lab. Carlsberg*, **23**, 289 (1940); (b) K. Linderstrøm-Lang and C. F. Jacobsen, *J. Biol. Chem.*, **137**, 443 (1941); (c) R. B. Simpson and H. A. Saroff, *J. Am. Chem. Soc.*, **80**, 2129 (1958).

(2) (a) J. R. Weisiger, W. Hausmann, and L. C. Craig, *ibid.*, 77, 3123 (1955); (b) I. M. Lockhart, E. P. Abraham, and G. G. F. Newton, *Biochem. J.*, **61**, 534 (1955); (c) L. C. Craig, W. Konigsberg, and R. J. Hill, "Ciba Foundation Symposium, Amino Acids and Peptides with Antimetabolic Activity," J. and A. Churchill, Ltd., London, 1958, p. 226.

(3) (a) D. F. W. Cross, G. W. Kenner, R. C. Sheppard, and C. E. Stehr, *J. Chem. Soc.*, 2143 (1963); (b) M. Bodanszky, *et al.*, *J. Am. Chem. Soc.*, **86**, 2478 (1964).

(4) E. H. White, F. McCapra, and G. F. Field, *ibid.*, **85**, 337 (1963).

(5) (a) M. Calvin in "Glutathione," S. Colowick, *et al.*, Ed., Academic Press Inc., New York, N. Y., 1954, p. 3; (b) G. Préaux and R. Lontie, *Biochem. J.*, **66**, 26P (1957); (c) D. Garfinkel, *J. Am. Chem. Soc.*, **80**, 4833 (1958); (d) R. B. Martin and J. T. Edsall, *Bull. soc. chim. biol.*, **40**, 1763 (1958); (e) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).

(6) R. E. Basford and F. M. Huennekens, *ibid.*, **77**, 3878 (1955).

(7) G. A. Snow, *J. Chem. Soc.*, 4080 (1954).

(8) H. N. Rydon, *Nature*, **182**, 928 (1958).

(9) (a) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, **83**, 4830 (1961); (b) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).

(10) H. A. Smith and G. Gorin, *ibid.*, **26**, 820 (1961).

(11) E. Felder and D. Pitrè, *Gazz. chim. ital.*, **89**, 1079 (1959). The authors state that hydrolysis of 2-methyl-Δ^2-thiazoline in 0.1 *N* HCl results in the accumulation of 2-methyl-2-hydroxythiazolidine in 36% yield. This conclusion appears wholly without foundation, in view of the work of Martin, *et al.*, (ref. 5e and 9).

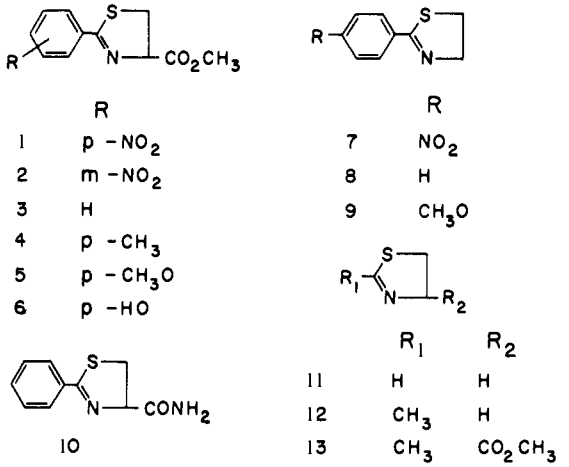


Figure 1.

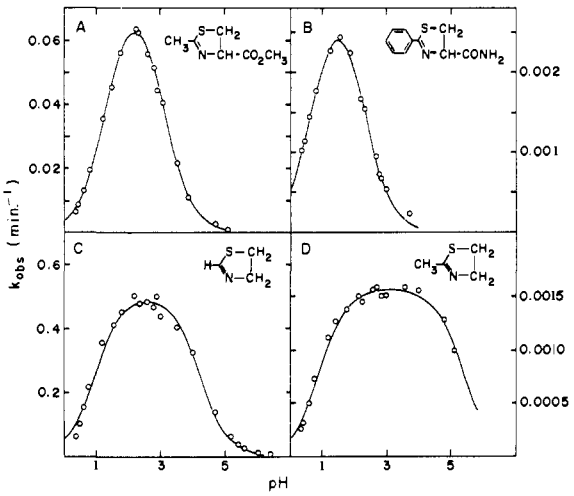


Figure 2. pH–rate profile for hydrolysis of thiazolines at 30°. Solid curves calculated by substituting constants of Table I into eq. 1. Ordinates: A, upper left; B, upper right; C, lower left; D, lower right.

rate constants for the processes described in Figure 4. The steps k_4 and k_6 are considered to proceed at a negligible rate in the initial stages of the reaction.[12]

$$k_{obsd} = \frac{k_1(H^+)[(k_3 + k_5)/k_2]}{[K_1 + (H^+)][(H^+) + (k_3 + k_5)/k_2]} \quad (1)$$

For each thiazoline (except **1**), the best values of the terms k_1, K_1, and $(k_3 + k_5)/k_2$ were obtained by fitting the observed rate constants to the assumed rate equation (eq. 1) by means of a least-squares method, using an IBM 709 computer.[13] These values are presented in the first three columns of Table I, together with the dissociation constants K_1 obtained for each compound by spectrophotometric titration (see Experimental). The solid lines drawn in Figures 2 and 3A represent the dependence of k_{obsd} upon pH calculated from eq. 1, employing the constants k_1, K_1, and $(k_3 + k_5)/k_2$ derived from the least-squares fit. The agreement between observation and theory is seen to be reasonable in

(12) The detailed derivation of eq. 1 is given in ref. 5e.

(13) The necessary computer program was obtained from Professor W. W. Cleland of the University of Wisconsin. The general principles of the iterative procedures employed in making least-square fits of kinetic data to assumed rate equations have been discussed in W. W. Cleland, *Nature*, **198**, 463 (1963), and G. N. Wilkinson, *Biochem. J.*, **80**, 324 (1961).

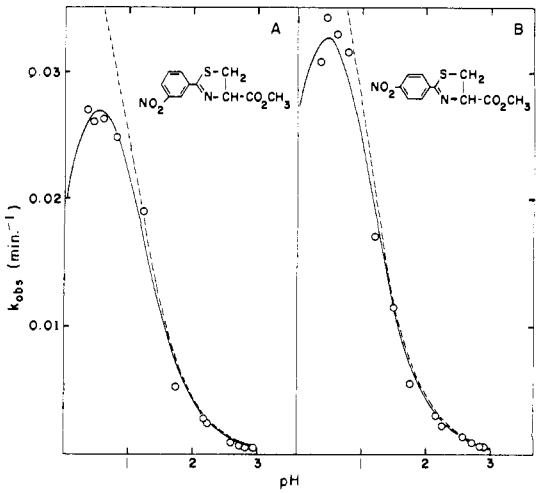


Figure 3. pH–rate profile for hydrolysis of nitrophenylthiazolines at 30°. Solid lines calculated by substituting constants of Table I into eq. 1. Dashed lines calculated by substituting constants of Table I into eq. 2.

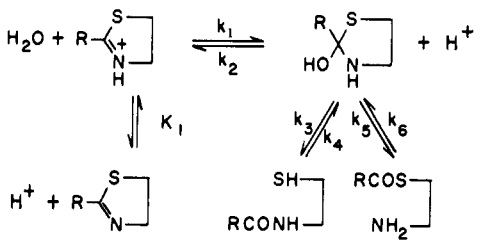


Figure 4. Mechanism of hydrolysis of Δ^2-thiazolines.

each case. Satisfactory comparison of observed rate constants to calculated values was also obtained for thiazolines **3–9**. For the *p*-nitrophenylthiazoline (**1**), the constants of eq. 1 were estimated by successive approximations and the selected values, shown in Table I, were used to calculate the solid curve of Figure 3B. The constants for 2-methylthiazoline (**12**) may be compared to those obtained by Martin[5e] at 25° (k_1 = 10.5 × 10^{-4} min.$^{-1}$, $(k_3 + k_5)/k_2$ = 0.10 *M*, and pK_1 = 5.22).

Table I. Rate Constants for the Hydrolysis of Thiazolines and Dissociation Constants of the Protonated Thiazolines[a,b]

Compd.	$k_1 \times 10^4$ min.$^{-1}$	$(k_3 + k_5)/k_2$, *M*	pK_1[c]	pK_1[d]
1	600	1.00	0.9	0.9
2	488	0.83	1.0	1.0
3	31.1	0.24	2.45	2.28
4	13.3	0.20	2.58	2.67
5	4.41	0.26	3.04	2.90
6	2.96	0.25	3.17	3.07
7	16.8	0.78	3.02	2.60
8	0.91	0.32	4.38	4.31
9	0.135	0.42	4.95	4.76
10	32.6	0.20	2.27	2.12
11	5080	0.12	4.23	*e*
12	15.8	0.13	5.39	5.25
13	805	0.05	3.06	3.13

[a] At 30° in 10% (v./v.) ethanol–water; μ = 0.9. [b] The constants of columns 2, 3, and 4 were obtained by least-squares analysis of the kinetic data, except for compound **1**. [c] Calculated from kinetic data. [d] Determined by spectrophotometric titration. [e] Not measured because of rapid hydrolysis.

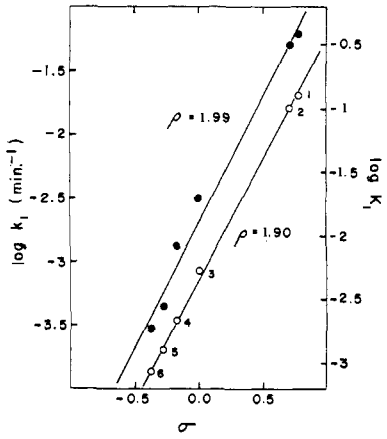


Figure 5. Dependence of the logarithm of the rate constants k_1 for the hydration of six 2-arylthiazolinium ions and of the logarithm of the dissociation constants K_1 of these thiazolinium ions upon the substituent constants σ: ● (log k_1), left ordinate; ○ (log K_1), right ordinate. Numbers refer to compounds of Figure 1.

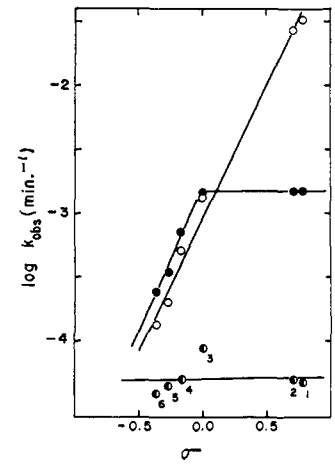


Figure 6. Dependence of the logarithm of k_{obsd} for the hydrolysis of six 2-arylthiazolines at three different pH values upon the substituent constants σ: ◐, pH 4.0; ●, pH 2.5; ○, pH 0.5. Numbers refer to compounds of Figure 1.

The rate constant k_1 for hydration of the thiazolinium ion exhibits a marked dependence upon the nature of the aryl substituent in a series of closely related 2-aryl-4-carboxythiazoline methyl esters (Table I, **1–6**). A moderately good correlation of log k_1 with the Hammett σ-constants[14] (ρ = 1.99) is shown in Figure 5. The use of σ^+ does not appreciably improve the fit.[15] The same figure depicts the good correlation of log K_1 for the thiazolinium ions with σ (ρ = 1.90).

The pronounced increase in k_1 with increasing electron-withdrawing nature of the aryl substituent is not mirrored by the behavior of k_{obsd}, which is rather more complex. The dependence of k_{obsd} upon the electronic character of the aryl substituent is seen, for three different pH values, in the Hammett plot of Figure 6. The values of k_{obsd} for pH 4.0 are extrapolated from the calculated curves based on eq. 1, since, for several of the compounds, rate measurements were not carried out above pH 3.5. It may be seen that, at pH 4.0, the rate hydrolysis is insensitive to the nature of the polar substituent (ρ = 0.02). At pH 2.5, a nonlinear ρ–σ relationship is observed, with k_{obsd} being strongly substituent dependent in compounds with electron-donating groups, and effectively constant in compounds with electron-withdrawing substituents. The marked dependence of k_1 on the polar character of the substituents (Figure 5) is reflected in k_{obsd} when the rate measurements are performed at pH 0.5 (ρ = 2.08). This interesting pH dependence of substituent effect is discussed further below.

It was anticipated that, at alkaline pH, Δ^2-thiazolines might exhibit a pH-independent hydrolysis reaction, such as is known to occur with 2-methyl-5,6-dihydro-1,3-thiazine,[9a] Schiff bases derived from aliphatic and aromatic amines,[16] and 2-methyloxazoline.[17] In the pH range 8.5 to 12.7, the disappearance of 2-methylthiazoline takes place at an essentially constant rate of about 16–19 × 10^{-4} min.$^{-1}$ at 78° ($t_{1/2}$ *ca.* 7 hr.). At 30°, the hydrolysis proceeds with an estimated half-life of 9–12 days in the same pH range. The possibility was considered that the slow reaction in the alkaline region represented nucleophilic displacement at position 5 of the thiazoline nucleus (to yield thionamide derivatives) rather than addition to the imine function.[18] The ultraviolet spectra of reaction mixtures, determined at various extents of completion of reaction, indicated that no thionamide was formed (or, at least, accumulated) from 2-methylthiazoline in aqueous alkaline medium.

Discussion

The results of the present study indicate that the mechanism of Figure 4, proposed[5e] to account for the characteristic bell-shaped rate–pH profile of the hydrolysis of 2-methylthiazoline, is probably a general one for Δ^2-thiazolines. Assumption of this mechanism leads to the prediction that k_{obsd} will vary with pH according to eq. 1. Least-squares analysis of the rate data obtained for a given thiazoline should therefore yield values of the constant terms k_1, K_1, and $(k_3 + k_5)k_2$, independent of any other assumptions or measurements. The kinetically derived values of K_1 may then be compared, where possible, to the dissociation constants of the thiazolinium ions determined by conventional procedures. This comparison is made in the last two columns of Table I. Agreement between kinetic and spectrophotometric pK values is satisfactory, the differences not exceeding 0.2 pH unit, except in one case (compound **7**).[19] Two factors may be responsible for these differences: (a) no correction has been made in the rate data for general catalytic effects by buffer species; general-base catalysis (in terms of protonated substrate) is expected on the alkaline side

(14) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 204.

(15) The deviations of the *p*-hydroxy and *p*-methoxy compounds being in the direction of σ^+, much improved correlation of log k_1 with substituent constants can be obtained by the method of Yukawa and Tsuno, [*Bull. Chem. Soc. Japan*, **32**, 965 (1959); **32**, 971 (1959)], with an assigned value of 0.38 to the parameter R. See also ref. 14, p. 211.

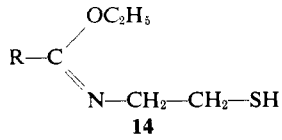
(16) (a) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962); (b) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963); (c) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).

(17) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, **41**, 1662 (1963).

(18) Nucleophilic displacement upon position 5 of the Δ^2-oxazoline ring system has been described by, *inter alia*, E. M. Fry, *J. Org. Chem.*, **15**, 438, 802 (1950); H. Behringer and K. Kuchinka, *Ann.*, **650**, 171 (1961). A general discussion of this phenomenon has been given by S. Hünig, *Angew. Chem. Intern. Ed. Engl.*, **3**, 548 (1964).

(19) Insufficient data were obtained for this substance in the pH region of its acid dissociation. This is probably the major cause of the sizable discrepancy.

of the pH profile, and has been observed with thiazolines,[5e,9b] Schiff bases,[16b,c] and imino esters,[20] but the corrections should be minor (less than 5%) at the low buffer concentrations employed here; (b) the presence of ethanol in the medium may complicate the solvolytic mechanism. Nucleophilic attack of ethanol on thiazolinium ion could lead to the imino ester **14**, which would undergo subsequent hydrolysis. The similarity



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of our rate data for 2-methylthiazoline (**12**) to those of Martin[5e] (reaction carried out in water) suggests that a pathway involving ethanol does not contribute significantly to the over-all rate of disappearance of the Δ^2-thiazolines.

The hydrolysis of Δ^2-thiazolines is thus accounted for in terms of rate-limiting attack of water upon protonated thiazoline on the alkaline side of the rate–pH profile. With decreasing pH, a transition occurs from rate-limiting attack of water to rate-limiting breakdown of the tetrahedral intermediate; the rate decrease at higher acidity is explicable by the decreasing concentration of the uncharged tetrahedral intermediate. Similar interpretations of bell-shaped (or more complex) rate–pH profiles have been presented for the hydrolysis of 2-methyloxazoline,[9b,21] a dihydrothiazine,[9a] and aliphatic Schiff bases.[16b,c] The considerable body of evidence which supports the postulated change in rate-limiting step with pH has been summarized by Jencks[22] and has also been discussed by Martin.[23]

The decrease in the rates of many hydrolytic reactions in moderately acidic solutions has frequently been explained on the basis of a decrease in the activity of water, which acts as both nucleophilic and proton transfer agent. This explanation appears valid for, *inter alia*, amide hydrolysis[24] and aromatic Schiff base hydrolysis.[16a] On the other hand, acid inhibition of the hydrolysis of 2-methylthiazoline[5e] and aliphatic Schiff bases[16b,c] seems adequately represented by the mechanism of Figure 4. With 2-methyloxazoline, rate decrease does not set in until acidities high enough to render unequivocal interpretation difficult; Greenhalgh, *et al.*,[17] favor explanation in terms of decreasing water activity, while Martin[9b,21] has proposed a mechanism analogous to that of Figure 4.

The 13 thiazolines of this study may be divided into three groups: (a) alkylthiazolines (**11–13**), with low[25] values of $(k_3 + k_5)/k_2$, for which acid inhibition is most likely the result of the operation of the mechanism of Figure 4; (b) arylthiazolines (**3–10**), characterized by intermediate values of the constant $(k_3 + k_5)/k_2$; while reasonably good agreement with eq. 1 was obtained on the acid side of the *p*H profiles, it is possible that the rate decrease is due in part to activity changes; (c) the nitrothiazolines **1** and **2**; no rate decrease is observed in solutions as acidic as pH 0.5 (Figure 3). The dashed lines of Figure 3 are calculated on the assumption that the rates of hydrolysis of these two compounds parallel the extent of thiazoline protonation (eq. 2). The negative deviations clearly exhibited

$$k_{obsd} = \frac{k_1(H^+)}{K_1 + (H^+)} \qquad (2)$$

by the rate data for the *m*-nitro thiazoline (Figure 3A) and possibly also for the *p*-nitro isomer (Figure 3B) show that a leveling off of the hydrolysis rate has occurred, which cannot be explained on the basis of complete protonation of the substrates. The nature of the factors responsible for this leveling effect cannot be stated from the available data; by analogy to the other substances of this study, it has been assumed that eq. 1 is valid for compounds **1** and **2** also.

Additional support for the proposed mechanism is obtained from the examination of substituent effects in 2-arylthiazolines. The calculated rate constants k_1 for attack of water on the fully protonated thiazoline show strong dependence on the nature of the polar substituent, with $\rho = 1.99$ (Figure 5). Hydrolysis of a series of aliphatic Schiff bases derived from substituted benzaldehydes exhibits similar substituent dependence ($\rho^+ = 1.71$) and is assumed to occur *via* an analogous mechanism.[16b] The apparently complex effect of substituents on the observed rates of thiazoline hydrolysis (Figure 6) is also in agreement with the two-step mechanism; at pH 4.0, the lack of dependence of rate on nature of the substituent results from cancellation of substituent effects on thiazoline protonation and hydration of thiazolinium ion. Polar factors which enhance attack of water ($\rho = 1.99$) decrease extent of thiazoline protonation to about the same degree ($\rho = 1.90$, in direction of dissociation). The insensitivity of the rates of acid-catalyzed benzamide hydrolysis to substituent nature has also been interpreted in terms of a cancellation of substituent effects on protonation and addition to the carbonyl group.[27] At pH 0.5, the observed rate depends markedly on substituent ($\rho = 2.08$). At this pH value, conversion of the tetrahedral intermediate to products is mainly rate limiting and the observed ρ-value is largely the result of substituent effects on the equilibrium concentration of intermediate. The nonlinear ρ–σ relationship seen at pH 2.5 could be interpreted as evidence for the two-step nature of the hydrolytic pathway and for transition from rate-limiting attack of water (with electron-withdrawing substituents) to rate-limiting breakdown of the intermediate (in the case of the electron-donating groups). Nonlinear Hammett relationships of this type have been employed as evidence for change in the rate-limiting step in Schiff base[16a] and semicarbazone[28] formation. It

(20) Unpublished experiments by Mr. Bruce Cunningham.

(21) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, 83, 4835 (1961).

(22) W. P. Jencks in "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p. 63.

(23) R. B. Martin, *J. Phys. Chem.*, **68**, 1369 (1964).

(24) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).

(25) The constant $(k_3 + k_5)/k_2$ determines the position of the midpoint of the descending limb on the acid side of the pH profile. A relatively low value of this term means that acid inhibition sets in at a relatively high pH. It is tempting to interpret variations in $(k_3 + k_5)/k_2$ in terms of effects on the partitioning of the tetrahedral intermediate. However, as pointed out by Zerner and Bender,[26] this term contains the "hidden" equilibrium constant for protonation of the tetrahedral intermediate. The relatively small variations in $(k_3 + k_5)/k_2$ shown in Table I thus reflect structural effects both on partitioning of the intermediate and on its protonation, factors which cannot be separated at present.

(26) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, 83, 2267 (1961), and especially footnote 37 therein.

(27) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, 38, 2271 (1960).

must be emphasized that incomplete cancelation of substituent effects on protonation and hydration in the case of the thiazolines with electron-donating substituents can result in a break in the ρ–σ plot. This alternative explanation may be the correct one for the compounds of this study; in the absence of other information, conclusion of a change in rate-limiting step based solely on nonlinear Hammett plots is unjustified.

In summary, the assumption of a generally valid mechanism is strengthened by: (a) quantitative agreement between the rate data for 13 thiazolines with widely differing substituents and the rate equation (1); (b) satisfactory comparison of thiazoline dissociation constants obtained by kinetic and spectrophotometric methods; (c) nature of substituent effects on the hydration step k_1 and on the observed hydrolysis rate at various pH values.

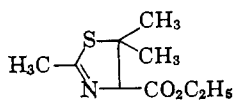
Considerable influence is exerted by structural factors upon the rate of hydration of thiazolinium ions. In the present series, the rate constant k_1 increases 38,000-fold in going from 2-*p*-methoxyphenyl-Δ^2-thiazoline (**9**) to Δ^2-thiazoline (**11**). It is possible to arrive at certain generalizations concerning structure–reactivity relationships.

(a) Within a series of ten 2-arylthiazolines, a satisfactory linear relation obtains between log k_1 and pK_1 of the thiazoline, *whether or not the thiazoline bears a substituent in the 4-position* (Figure 7, curve A). The expression

$$\log k_1 = -0.91\mathrm{p}K_1 - 0.48$$

acceptably correlates the rates of hydration of three 2-arylthiazolines (**7**–**9**), six 2-arylthiazolines possessing an esterified carboxyl group in the 4-position (**1**–**6**), and one thiazoline with a carboxamide group in the 4-position (**10**). The principal manner through which *neutral*[29] 4-substituents affect the rate of thiazoline hydrolysis seems to be by inductively altering electronic density at the site of nucleophilic attack, an effect which is quantitatively reflected in the thiazolinium ion dissociation constant.

(b) Similar conclusions may be tentatively drawn for 2-methyl-Δ^2-thiazolines with 4- or 5-substituents. Curve B in Figure 7 has been arbitrarily drawn with a slope equal to that of curve A. The hydration rate constants for the 2-methylthiazolines of this study (**12** and **13**) and of the more extensively substituted thiazoline **15**[9b,30] appear to vary with pK in manner



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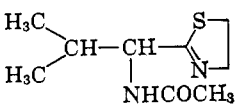

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parallel to that of 2-arylthiazolines. Consequently, a 2-methylthiazoline is about 250 times more reactive than a 2-arylthiazoline of the same pK. The greater stability of the arylthiazoline presumably both reflects

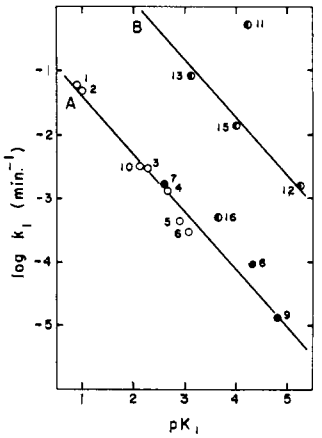

Figure 7. Dependence of the logarithm of rate constants k_1 for the hydration of thiazolinium ions upon the pK_1 of the thiazolinium ions: ●, 2-arylthiazolines; ○, 2-aryl-4-substituted thiazolines; ◐, aliphatic thiazolines. Numbers refer to compounds of Figure 1 (**1**–**13**) and to text (**15** and **16**).

the increased resonance stabilization of starting material relative to transition state in the aryl series and steric inhibition of nucleophile approach. Replacement of the 2-methyl group by a branched substituent, as in the thiazoline **16** (a structure related to bacitracin A[31]), significantly increases resistance to hydrolysis.[9a] The steric consequence of this structural change results in stabilization by a factor of about 100, relative to a 2-methylthiazoline of the same pK.[30]

(c) Thiazolines bearing no substituents in the 2-position. Only one representative of this interesting class of compounds was studied. Δ^2-Thiazoline (**11**) is the most reactive thiazoline encountered in this work ($t_{1/2}$ at pH 3 and 30° is 80 sec.), and is hydrolyzed about 50 times more rapidly than would be a 2-methylthiazoline of the same pK. Its instability prevented determination of its pK by conventional techniques. The inferred kinetic dissociation constant of 4.23 is about one unit lower than that of 2-methylthiazoline. This difference is of the expected magnitude (*cf.* imidazole and 2-methylimidazole[32]). Little information could be found in the literature concerning the behavior of 2-unsubstituted thiazolines in aqueous media. Cavallini, *et al.*,[33] have reported the preparation of the rather unstable Δ^2-thiazoline-4-carboxylic acid, obtained by acid-catalyzed cyclization of N-formylcysteine. Evidence for the ready hydrolysis of the N-methyl derivative of Δ^2-thiazoline (N-methylthiazolinium methyl sulfate) has been described.[34]

Zerner and Bender[26] have given a valuable discussion of five kinetic schemes which lead to bell-shaped rate–pH profiles. Thiazoline hydrolysis conforms to scheme v in their paper. It should be noted that the symmetry of the denominator of the rate equation for thiazoline hydrolysis (eq. 1 of this paper) introduces an ambiguity in the initial interpretation of the rate data. In general terms, eq. 1 may be written as

(28) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).

(29) Substituent groups such as the carboxyl function, capable of undergoing ionization, influence the rates and pH profile of thiazoline hydrolysis in a complex fashion, the study of which will be presented in a future communication.

(30) The rate data reported by Martin[9] were obtained at 25° rather than at 30°. Correction for the temperature difference (the rates should probably be increased by about 50%) would improve the fit of **15** to curve B and reduce the steric effect in **16** to a factor of about 50.

(31) W. Stoffel and L. C. Craig, *J. Am. Chem. Soc.*, 83, 145 (1961).

(32) T. C. Bruice and G. L. Schmir, *ibid.*, **80**, 148 (1958).

(33) D. Cavallini, B. Mondovi, and C. De Marco, *Experientia*, 13, 436 (1957).

(34) W. H. Hafferl, R. E. Lundin, and L. L. Ingraham, *Biochemistry*, 3, 1072 (1964). No rate data are given in this paper. Comparison of the rates of hydrolysis of 2-methylthiazoline and its N-methyl derivative,[9a] together with the known rate of hydrolysis of Δ^2-thiazoline (Table I), leads to an estimated half-life of about 8 min. for the N-methyl-Δ^2-thiazolinium ion in weakly acidic solution at 30°.

$$k_{obsd} = \frac{A(H^+)}{[B + (H^+)][(H^+) + C]}$$

As discussed above, analysis of the pH profile yields three constants, two of which correspond to the constants of the denominator. Only chemical intuition or independent pK determination, however, allows a choice between the constants B and C as the dissociation constant of the thiazolinium ion.

Two of the kinetic schemes of Zerner and Bender[26] involve the observation of bell-shaped curves as the result of the reaction between a general acid and a general base. A special case of this formulation exists when the general acid and the general base are simply members of the same conjugate acid–base pair. The bell-shaped curve obtained is thus the result of the ionization of a single group, rather than the ionization of two groups, as is commonly assumed in interpretation of such data. An example of this situation is found in the aminolysis of phenyl acetate by methoxylamine, which is catalyzed by the conjugate acid of methoxylamine.[35] A more complex system where the ionization of a (presumably) single group has led to the observation of a bell-shaped rate–pH profile has been described by Bright in an investigation of the mechanism of the β-methylaspartase reaction.[36] The rate of enzyme-catalyzed exchange of solvent hydrogen into deuterated β-methylaspartate varies with pH as a bell-shaped curve. It should be emphasized that a bell-shaped curve is expected for the exchange reaction only in the presence of a net over-all reaction.

The rate of hydrolysis of 2-methylthiazoline is independent of pH in the range 8.5–12.7. This finding is consistent with either a rate-limiting addition of water to thiazoline in free base form or with the kinetically indistinguishable attack of hydroxide ion on thiazolinium ion. It is proposed that the latter mechanism accounts for the pH-independent reaction of 2-methylthiazoline, by analogy to the conclusions drawn for the alkaline hydrolysis of Schiff bases.[16] This mechanism is described in eq. 3 and 4,[37] where it is assumed that $K_1 >> [H^+]$, and that the reverse re-

$$TH^+ + OH^- \underset{k_8}{\overset{k_7}{\rightleftharpoons}} \text{products} \qquad (3)$$

$$k_{obsd} = \frac{k_7 K_w}{K_1} \qquad (4)$$

action (step k_8) may be neglected. The approximate half-life of 10 days at 30° for the pH-independent reaction of 2-methylthiazoline (k_{obsd} *ca.* 0.4×10^{-4} min.$^{-1}$) yields an estimated value of 1.6×10^4 M^{-1} min.$^{-1}$ for k_7, the second-order rate constant for attack of hydroxide ion on protonated thiazoline. The ratio of the rates of nucleophilic hydroxide attack to water attack on thiazolinium ion (k_7/k_1) is thus 1×10^7 M^{-1}. Previous studies have shown that this ratio varied from 10^7 to 10^8 M^{-1} for aldehydic Schiff bases,[16a,b] a dihydrothiazine[9a] and the N-methylthiazolinium ion.[9a] With benzophenone Schiff bases,[16c] the rate ratio was in the range 10^6 to 10^7 M^{-1}. Employing the value of 10^8 M^{-1} as an upper limit for the ratio k_7/k_1, the maximum observed rate constant to be expected for the pH-independent alkaline hydrolysis of all the thiazolines of this study may be estimated from eq. 4 and the known values of k_1 (Table I). Extremely slow hydrolysis ($t_{1/2}$ of the order of 1 year) is thus anticipated for all the 2-arylthiazolines, largely as a result of the very small concentrations of thiazolinium ion present at alkaline pH. With the more basic and intrinsically more reactive aliphatic thiazolines, hydrolysis at alkaline pH should be detectable.

(35) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960).

(36) H. Bright, *J. Biol. Chem.*, **239**, 2307 (1964).

(37) TH^+ = thiazolinium ion; K_w = ion product of water; K_1 = acid dissociation constant of thiazolinium ion.

Experimental[38]

L-*Cysteine methyl ester hydrochloride* was prepared in 75–85% yield from L-cysteine or L-cysteine hydrochloride monohydrate by treatment with hot methanolic HCl. After recrystallization from methanol–ether, the product had m.p. 142–143°, $[\alpha]^{30}D$ −2.4° (*c* 10, methanol) (lit.[39] m.p. 140°, $[\alpha]^{20}D$ −2.9° (*c* 10, methanol)).

2-(p-Nitrophenyl)-4-carboxy-Δ²-thiazoline Methyl Ester (**1**). A solution of 2.54 g. (14 mmoles) of methyl *p*-nitrobenzimidate[40] in 11 ml. of methanol was combined with a solution of 2.41 g. (14 mmoles) of L-cysteine methyl ester hydrochloride in an equal volume of methanol, and the mixture was kept at room temperature for 48 hr. The resulting suspension was poured into 75 ml. of cold water, stirred briefly, and the crystalline product was collected by filtration and dried *in vacuo* over P_2O_5 (3.38 g., 90%, m.p. 102–105°). Recrystallization from methanol yielded long silky yellow needles of m.p. 106–108°. Prior to analysis, the product was dried at 80° *in vacuo* over P_2O_5, $[\alpha]^{30}D$ 0.0° (*c* 3, N,N-dimethylformamide).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S$ (266.27): C, 49.60; H, 3.78; N, 10.52; S, 12.04. Found: C, 49.63; H, 3.68; N, 10.50; S, 12.11.

The absence of optical rotation suggests that the product underwent racemization, which would be expected to occur with great facility with this compound.

L-*2-(m-Nitrophenyl-4-carboxy-Δ²-thiazoline Methyl Ester* (**2**). This compound was prepared in 87% yield from methyl *m*-nitrobenzimidate[41] by the method used for **1** and melted at 98–99°. Prior to analysis, the product was dried at 56° *in vacuo* over P_2O_5, $[\alpha]^{30}D$ 25.8° (*c* 3.1, N,N-dimethylformamide).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S$ (266.27): C, 49.60; H, 3.78; N, 10.52; S, 12.04. Found: C, 50.06; H, 3.88; N, 10.60; S, 12.15.

L-*2-Phenyl-4-carboxy-Δ²-thiazoline Methyl Ester* (**3**). A solution of 4.5 g. (30 mmoles) of ethyl benzimidate[42] in 3 ml. of methanol was added to a solution of 5.10 g. (30 mmoles) of L-cysteine methyl ester hydrochloride in 20 ml. of methanol, and the mixture was kept for 16 hr. at room temperature. A crystalline deposit was collected by filtration and discarded. The

(38) All melting points are uncorrected. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ultraviolet spectra were determined by means of a Perkin-Elmer Model 350 recording spectrophotometer. Optical rotations were measured with a Zeiss Circle polarimeter.

(39) L. Zervas and D. Theodoropoulos, *J. Am. Chem. Soc.*, **78**, 1359 (1956).

(40) W. Hilpert, *Am. Chem. J.*, **40**, 150 (1908).

(41) H. I. Schlesinger, *ibid.*, **39**, 759 (1908).

(42) D. F. Elliott, *Biochem. J.*, **45**, 429 (1949).

yellow filtrate was concentrated *in vacuo* to a mobile oil. The additional solid which precipitated on addition of dry ether was also discarded and the ethereal filtrate was concentrated to an oil which crystallized on cooling and triturating with petroleum ether. The product (5.68 g., 86%) had m.p. 40–41°, which increased to 41–43° on recrystallization from cyclohexane and drying over P_2O_5 *in vacuo* at room temperature, $[\alpha]^{30}D$ +39.5° (*c* 3, CH_3OH).

Anal. Calcd. for $C_{11}H_{11}NO_2S$ (221.27): C, 59.69; H, 5.01; N, 6.33; S, 14.48. Found: C, 59.81; H, 4.90; N, 6.16; S, 14.67.

When the above procedure was modified by replacing ethyl benzimidate by an equimolar mixture of ethyl benzimidate hydrochloride and triethylamine, a partially racemized product was obtained in 72% yield. Fractional crystallization from cyclohexane afforded pure racemic 2-phenyl-4-carboxy-Δ^2-thiazoline methyl ester,[43] m.p. 68–69°.

DL-*2-Phenyl-4-carboxy-*Δ^2*-thiazoline Methyl Ester.* A solution of 550 mg. (2.5 mmoles) of **3** and of 250 mg. (2.5 mmoles) of triethylamine in 13 ml. of methanol was kept at room temperature for 18 hr. After evaporation of the solvent *in vacuo*, the residue was dissolved in benzene and the benzene was removed at reduced pressure. The crystalline product was triturated with petroleum ether, collected by filtration (520 mg., 95%, m.p. 66–68°), and recrystallized from cyclohexane, the melting point increasing to 68–69° (lit.[43] m.p. 69°), $[\alpha]^{30}D$ 0.0° (*c* 1, CH_3OH).

Anal. Calcd. for $C_{11}H_{11}NO_2S$ (221.27): C, 59.69; H, 5.01; N, 6.33; S, 14.48. Found: C, 59.70; H, 5.05; N, 6.14; S, 14.30.

L-*2-(p-Tolyl-4-carboxy-*Δ^2*-thiazoline Methyl Ester* (**4**). To a solution of 11.7 g. (0.1 mole) of *p*-tolunitrile in 4 ml. of anhydrous ether was added a cold mixture of 4.2 g. (0.13 mole) of methanol and 4 g. (0.11 mole) of hydrogen chloride. The reaction mixture was kept at 5°. Deposition of colorless crystals began the following day. After 13 days, the imino ester hydrochloride (17.8 g., 96%) was collected, washed with anhydrous ether, and dried over KOH pellets. It melted at 127–129° with resolidification and further melting at 160–162°.

Methyl *p*-toluimidate was prepared as a colorless oil by treatment of its hydrochloride salt with cold, aqueous potassium carbonate and extraction into ether. The imino ester was used without further purification for the next step.

A solution of 1.70 g. (11.4 mmoles) of methyl *p*-toluimidate and of 1.95 g. (11.4 mmoles) of L-cysteine methyl ester hydrochloride in 10 ml. of methanol was kept at room temperature for 16 hr. The methanolic solution was decanted from the deposited crystals of NH_4Cl and concentrated to dryness *in vacuo*. The residue was taken up in ether and the solution was washed with water and twice with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. Crystallization from cyclohexane yielded 1.58 g. (61%), m.p. 39–41°. Two recrystallizations from the same solvent raised the m.p. to 42–43°, $[\alpha]^{30}D$ +32.8° (*c* 3, CH_3OH).

Anal. Calcd. for $C_{12}H_{13}NO_2S$ (235.29): C, 61.23; H, 5.57; N, 5.95; S, 13.62. Found: C, 61.48; H, 5.49; N, 5.78; S, 13.86.

L-*2-(p-Methoxyphenyl)-4-carboxy-*Δ^2*-thiazoline Methyl Ester* (**5**). Methyl *p*-methoxybenzimidate was prepared by the method used for the synthesis of methyl *p*-toluimidate. The crystalline imino ester obtained on evaporation of its ethereal solution had m.p. 32–34°.

The thiazoline was prepared according to the procedure used for **4**. The crude product (3.85 g., 77%) was crystallized from cyclohexane. It was further purified by three recrystallizations from benzene–*n*-pentane, and melted at 70–72°, $[\alpha]^{30}D$ +24.4° (*c* 3, CH_3OH).

Anal. Calcd. for $C_{12}H_{13}NO_3S$ (251.29): C, 57.34; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.44; H, 5.47; N, 5.54; S, 12.45.

L-*2-(p-Hydroxyphenyl)-4-carboxy-*Δ^2*-thiazoline Methyl Ester* (**6**). Methyl *p*-hydroxybenzimidate was prepared by the method used for the synthesis of methyl *p*-toluimidate. The imino ester hydrochloride had m.p. 168–170° while the crystalline imino ester melted at 157–158°.

The thiazoline was prepared in 77% yield by the method used for **4**. Two recrystallizations from benzene–cyclohexane yielded fine needles which sintered at 115° and melted at 165–167°, $[\alpha]^{30}D$ +19.2° (*c* 3, CH_3OH).

Anal. Calcd. for $C_{11}H_{11}NO_3S$ (237.27): C, 55.66; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.57; H, 4.79; N, 5.85; S, 13.35.

2-(p-Nitrophenyl)-Δ^2*-thiazoline* (**7**) was prepared in 80% yield from methyl *p*-nitrobenzimidate and cysteamine hydrochloride by the method described for **1**. After two recrystallizations from methanol, the product had m.p. 146.5–148° (lit.[44] m.p. 156–157°).

Anal. Calcd. for $C_9H_8N_2O_2S$ (208.23): C, 51.91; H, 3.87; N, 13.46; S, 15.40. Found: C, 51.58; H, 3.73; N, 13.21; S, 15.56.

2-Phenyl-Δ^2*-thiazoline* (**8**) was prepared according to Kuhn and Drawert.[45] The major fraction distilled at 118–119° (3.2 mm.); the picrate had m.p. 173.5–175° (lit.[45] m.p. 175–176°). The perchlorate salt was prepared by adding slowly an ethereal solution of **8** to a mixture of 70% aqueous $HClO_4$ in ether containing just enough ethanol to prevent phase separation. After recrystallization from ethanol–ether, the perchlorate had m.p. 128.5–129°.

Anal. Calcd. for $C_9H_9ClNO_4S$ (263.70): C, 40.99; H, 3.82; Cl, 13.45. Found: C, 41.47; H, 3.85; Cl, 13.76.

2-(p-Methoxyphenyl)-Δ^2*-thiazoline* (**9**) was prepared from methyl *p*-methoxybenzimidate and cysteamine hydrochloride by the method used for **4**. The crude product, obtained in 77% yield, melted at 52–54° (lit.[46] m.p. 54.5°) and yielded a picrate of m.p. 190–191.5° (lit.[46] m.p. 187°). To remove a persistent colored impurity, the thiazoline was converted in 92% yield to its perchlorate salt, m.p. 167–167.5°, as described for **8**.

Anal. Calcd. for $C_{10}H_{12}ClNO_5S$ (293.73): C, 40.88; H, 4.12; Cl, 12.08. Found: C, 40.90; H, 3.88; Cl, 12.52.

(43) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 2071 (1951).

(44) S. Babcock and R. Adams, *J. Am. Chem. Soc.*, **59**, 2260 (1937).

(45) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).

(46) P. Rehländer, *Ber.*, **27**, 2154 (1894).

2-Phenyl-4-carboxamido-Δ^2-thiazoline (**10**). Gaseous ammonia was passed into a cold solution of 1 g. (4.5 mmoles) of **3** in 25 ml. of methanol for 35 min. After 1 hr., the deposited colorless crystals (800 mg., 86%) were collected, and melted at 185–186°. Two recrystallizations from methanol–benzene raised the melting point to 186.5–187.5°, $[\alpha]^{30}D$ 0.0° (*c* 3.03, N,N-dimethylformamide).

Anal. Calcd. for $C_{10}H_{10}N_2OS$ (206.26): C, 58.21; H, 4.88; N, 13.58; S, 15.54. Found: C, 58.48; H, 4.73; N, 13.61; S, 15.77.

It is probable that ammonia-catalyzed racemization took place during the ammonolysis of the optically active ester.

Δ^2-Thiazoline (**11**) was prepared from N-formylethanolamine according to Wenker,[47] and distilled at 34° (12 mm.); picrate, m.p. 150–153° (lit.[47] m.p. 150–151°). The infrared spectral data were in essential agreement with those reported.[34]

2-Methyl-Δ^2-thiazoline (**12**) (Aldrich) distilled at 32–33° (15 mm.); picrate, m.p. 170.5–172.5° (lit.[45] m.p. 171–172°). The perchlorate salt was prepared in 85% yield as described for **8**. Two recrystallizations from ethanol–ether yielded colorless, nonhygroscopic crystals, m.p. 127–128°.

Anal. Calcd. for $C_4H_8ClNO_4S$ (201.64): C, 23.83; H, 4.00; Cl, 17.60. Found: C, 24.25; H, 3.98; Cl, 17.53.

The *p*-toluenesulfonate salt was prepared by adding a solution of 205 mg. (2.01 mmoles) of **12** in 10 ml. of anhydrous ether to a solution of 760 mg. (4 mmoles) of *p*-toluenesulfonic acid monohydrate in 20 ml. of anhydrous ether. After brief cooling, the supernatant liquid was discarded and the residual oil was crystallized from ethanol–ether at room temperature, yielding 458 mg. (83%), m.p. 118–120°. Recrystallization from ethanol–ether at room temperature raised the melting point to 121–122°.

Anal. Calcd. for $C_{11}H_{15}NO_3S_2$ (273.36): C, 48.32; H, 5.54; S, 23.46. Found: C, 48.12; H, 5.17; S, 23.92.

L-*2-Methyl-4-carboxy-Δ^2-thiazoline Methyl Ester* (**13**). To a solution of 1.85 g. (15 mmoles) of ethyl acetimidate hydrochloride[48] and of 1.515 g. (15 mmoles) of triethylamine in 10 ml. of methanol was added a solution of 2.57 g. (15 mmoles) of L-cysteine methyl ester hydrochloride in 10 ml. of methanol. The reaction mixture was kept at room temperature for 16 hr., then chilled for 4 hr. After removal of precipitated NH_4Cl, the solvent was removed *in vacuo*. The residual oil was taken up in 40 ml. of anhydrous ether, and some insoluble material was discarded by filtration. After drying over $MgSO_4$, the solvent was removed *in vacuo*, affording 2.13 g. (86%) of the thiazoline as a mobile, colorless oil which distilled at 88–90° (2.5 mm.), $[\alpha]^{31}D$ 100° (*c* 3.7, 1 *M* sodium phosphate buffer, pH 6.8).

Anal. Calcd. for $C_6H_9NO_2S$ (159.20): C, 45.26; H, 5.70; N, 8.80; S, 20.14. Found: C, 45.20; H, 6.13; N, 8.77; S, 19.98.

The perchlorate was prepared in 88% yield as described for **8** and melted at 87–90°, $[\alpha]^{31}D$ 122° (*c* 3.1, calculated on basis of thiazoline free base, 1 *M* sodium phosphate buffer, pH 6.8).

(47) H. Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).
(48) S. M. McElwain and J. W. Nelson, *ibid.*, **64**, 1825 (1942).

Anal. Calcd. for $C_6H_{10}ClNO_6S$ (259.67): C, 27.75; H, 3.88; Cl, 13.65. Found: C, 27.71; H, 4.16; Cl, 13.50.

The preparation of the hydrochloride of **13** has been previously reported.[10]

Kinetic Measurements. The hydrolysis of Δ^2-thiazolines in acidic solution was studied at 30° in 10% (v./v.) ethanol–water, at 0.9 *M* ionic strength maintained with added KCl. Constant pH was kept with dilute solutions (0.02–0.05 *M*) of sodium chloroacetate, sodium acetate, or sodium phosphate buffers for the region of pH 2–7, while HCl solutions were used below pH 2. Most reactions were carried out in stoppered volumetric flasks immersed in a constant temperature bath at 30°. Aliquots were withdrawn at appropriate times and the decrease in optical density resulting from hydrolysis was followed with a Beckman DU spectrophotometer. Very slow reactions were carried out in sealed ampoules. For rapid hydrolyses (half-life 30 min. or less), the reaction solution was rapidly mixed and transferred immediately into a rectangular, 4-ml. Beckman cuvette inserted in a water-jacketed cuvette holder maintained at 30° by means of a circulating bath.

The rates of hydrolysis were conveniently determined by measuring the decrease in the characteristic long wave-length absorption of protonated thiazolines (Table II). With the exception of the nitrothiazolines (discussed below), the wave length selected to follow hydrolysis (Table II, column 6) was one where the hydrolysis products exhibited negligible absorption. No such region of the ultraviolet spectrum was found with the nitrothiazolines. The wave length of 272 mμ was chosen to study the hydrolysis of the *p*-nitro-

Table II. Ultraviolet Spectral Data for Thiazolines and Thiazolinium Ions and Wave Lengths Used for Kinetic and p*K* Measurements

	— Thiazoline[a] —		— Thiazolinium ion[b] —			
Compd.	λ_{max}, mμ	ϵ_{max}	λ_{max}, mμ	ϵ_{max}	$\lambda_{hydrolysis}$, mμ[c]	λ_{pK}, mμ
1	277	15,200	277	18,000	272	277
2	233	22,200	253	21,000	244, 260	260
3	245	15,200	277	19,200	300	290
4	256	14,500	293	20,200	300, 310	290
5	270	18,600	327	25,600	328	328
6	270	17,300	326	23,600	328	228
7	278	14,900	274	19,700	272	278
8[d]	242	13,900	270	17,100	300	280
9[d]	266	28,600	314	24,000	330	328
10	246	13,500	275	16,300	300	290
11	251	2,840	267	5,330	260, 276	[e]
12[d,f]	246	2,520	261	5,000	260	270
12[g]	248	3,100	262	6,200		
13[d,h]	247	2,640	260	4,300	260, 270	270

[a] Solvent was 10% ethanol–water for thiazoline free bases, except for **11** where 95% ethanol–water was used. Where thiazolinium salts were employed, solvent was 10% ethanol–water buffered at pH 7 with sodium phosphate. [b] All solutions contained 10% ethanol–water acidified to the following final concentrations of HCl: **9** and **13**, 0.6 *N*; **7** and **12**, 1.8 *N*; **1**, **2**, **4**–**6**, and **8**, 3.6 *N*; **3**, 5.4 *N*; and **11**, 6 *N*. [c] Where more than one wave length was used, determined rate constants were independent of wave length of measurement. [d] Perchlorate salt. [e] p*K* not determined. [f] Spectral data almost identical with those reported for aqueous solution.[5e] [g] *p*-Toluenesulfonate salt. [h] Free base gave identical spectral data.

phenylthiazolines **1** and **7** on the basis of the observation that the molar extinction coefficients of *p*-nitrobenzamide derivatives and of *p*-nitrobenzoyl thiol esters (both potential hydrolysis products) were nearly identical in this spectral region. Thus, the optical density at completion of reaction would be nearly independent of the nature of the products (N-acyl- or S-acylcysteamines) and unaffected by possible S → N acyl transfer at the higher pH values. With the *m*-nitrophenylthiazoline **2**, it was noted that the rapidly reached final optical densities below pH 1 were significantly higher than the slowly attained final values above pH 2. It was assumed that the hydrolysis product in strongly acidic solution was mainly the S-acylcysteamine, which rearranged rapidly above pH 2 to the N-acylcysteamine of lesser extinction. In the pH range 1–2, "final" optical densities drifted slowly downwards, presumably as a result of slow rearrangement, and rate constants for hydrolysis were not evaluated in this pH region.

In all cases, initial thiazoline concentration was chosen so as to give an initial optical density of 1.2 (concentrations varied from 5×10^{-5} to 5×10^{-4} *M*). The pseudo-first-order rate constants were calculated using the expression

$$k = \frac{2.303}{t} \log \frac{D_i - D_f}{D - D_f}$$

where D_f = optical density at infinite time, D_i = initial optical density, and D = optical density at time t.

The hydrolysis of 2-methylthiazoline in alkaline solution at 78° was carried out using the sealed-ampoule technique previously described.[49] The quenched reaction mixture was acidified with aqueous HCl and the absorbance of remaining thiazolinium ion was measured immediately at 275 mμ. Alternatively, the decrease in absorbance at 250 mμ was measured on the sample prior to acidification. Rate constants were calculated from the integrated first-order rate equation; the results of measurements at the two wave lengths were in good agreement.

pK Determinations. With the exception of the *p*-nitro-substituted derivatives, the ultraviolet spectra of the thiazolines of this study exhibit pronounced bathochromic shifts upon protonation (Table II). The changes in absorbance of thiazoline solutions as a function of *p*H were measured at a suitable wave length (Table II, last column) and the resulting data were fitted to the Henderson–Hasselbalch expression. The calculated p*K* values are listed in Table I. The increase in extinction near the wave length of maximum absorption which occurred upon protonation of the *p*-nitrophenylthiazolines **1** and **7** allowed spectrophotometric determination of their p*K* also.

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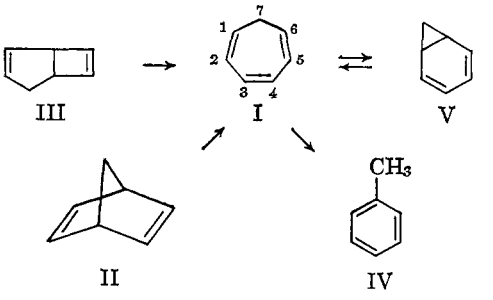
Communications to the Editor

New Thermal Rearrangements of Tropilidenes[1]

Sir:

Tropilidene (I) is connected by thermal pathways of carbon skeletal rearrangement to norbornadiene (II),[2–6] bicyclo[3.2.0]heptadiene (III),[7] toluene (IV),[2–6,8] and probably norcaradiene (V).[9,10] Overlaid upon these relatively deep-seated changes are the superficial thermal 7 → 4 hydrogen shifts which disperse the hydrogens over the carbon framework.[11] We report now two new intramolecular thermal transformations of the tropilidene skeleton, one of which leads to rearranged tropilidenes and the other to 1,4-cyclohexadienes.



Although the 7 → 4 hydrogen shift can be blocked by 7,7-disubstitution, detection of a carbon skeletal rearrangement in products retaining the tropilidene ring

(1) We are indebted to the Camille and Henry Dreyfus Fund and to the Army Research Office—Durham for support of this work.

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