Oxazolidine Hydrolysis. The Participation of Solvent and Buffer in Ring Opening

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Abstract: The rates of hydrolysis of a series of 2-(substituted phenyl)-3-ethyloxazolidines have been determined in water. At high pH where the compounds are predominantly in the neutral form, the observed rate constants for aldehyde formation are nearly independent of pH and are correlated well with σ, the value of ρ being -1.1. In moderately concentrated HCl solutions two reactions can be detected, a very rapid formation of an intermediate which absorbs strongly in the region from 325 to 280 mμ, and the much slower hydrolysis of this intermediate to give the aldehyde product. These two reactions must correspond to ring opening and hydrolysis of an intermediate cationic Schiff base. Increasing the acid concentration slows the rate of ring opening considerably; a plot of log k_{obsd} *vs.* log a_{H_2O} is curved with high initial slope. The value of ρ for this reaction measured in 3.57 *M* HCl is $+1.6$. Negative values of ΔS^* were found for cleavage of 2-phenyl-3-ethyloxazolidine. The rate of ring opening of 2-(*p*-methoxyphenyl)-3-ethyloxazolidine proceeds 2.65 times slower in D_2O than H_2O. Thus, all of the evidence is consistent with participation of solvent in ring opening. Acetate and formate buffers also catalyze ring opening.

The generally accepted mechanism for the acid-catalyzed hydrolysis of acetals involves a fast preequilibrium protonation of the substrate followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion.[1] If the rate-determining step of the hydrolysis of an acetal or analogous carbonyl derivative could be shown to proceed with participation by solvent or buffer then it should be possible to determine the factors responsible for this mechanism difference.[2] Such a finding would not only be of importance to a more thorough understanding of the mechanism of the acid-catalyzed reactions but might also lead to greater insight into the mechanistic possibilities which glycosidic enzymes could be employing since it would seem likely that functional groups at the active sites of these enzymes are actively involved in the bond-breaking process. It was thought that it would be of interest to study the hydrolysis of substituted oxazolidine derivatives since these compounds are completely protonated at moderate acid concentrations. The reactions can, therefore, be studied without complications arising from a preequilibrium protonation step. It has indeed been found that the ring-opening reaction with these compounds involves participation by solvent and is buffer catalyzed.

Experimental Section

Materials. Oxazolidines were prepared by refluxing in benzene equivalent amounts of the appropriately substituted benzaldehyde and N-ethylethanolamine. Substitution of the nitrogen precludes Schiff base formation. Water was continuously removed from the reaction by azeotropic distillation with the benzene. After collection of a theoretical amount of water, the benzene was removed by flash evaporation, and the liquid residue was distilled.

2-(*p*-Methoxyphenyl)-3-ethyloxazolidine had bp 113° (1.0 mm), $n^{23.5}D$ 1.5272. *Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.89; H, 8.32; N, 6.77.

2-(*p*-Methylphenyl)-3-ethyloxazolidine[3] had bp 84–86° (0.8 mm), $n^{23.5}D$ 1.5183.

2-Phenyl-3-ethyloxazolidine[3] had bp 67–68° (0.5 mm), $n^{22.5}D$ 1.5211.

2-(*p*-Chlorophenyl)-3-ethyloxazolidine had bp 103–105° (1.0 mm), $n^{22.5}D$ 1.5325. *Anal.* Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.12; H, 6.84; Cl, 17.08; N, 6.39.

2-(*m*-Chlorophenyl)-3-ethyloxazolidine had bp 92–93° (0.9 mm), $n^{25}D$ 1.5331. *Anal.* Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.34; H, 6.57; Cl, 16.65; N, 6.24.

2-(*p*-Nitrophenyl)-3-ethyloxazolidine had bp 126° (0.8 mm), $n^{23.5}D$ 1.5481. *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.60; H, 6.51; N, 12.63.

2-Phenyl-2-methyl-3-ethyloxazolidine (prepared using toluene as the solvent) had bp 88–90° (2.2 mm), $n^{24}D$ 1.5182. *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.11; H, 8.94; N, 7.34.

The Schiff bases of substituted benzaldehydes and ethanolamine were prepared by the same method.

***p*-Methoxybenzylideneethanolamine** had bp 139–139.5° (1.2 mm), $n^{25.8}D$ 1.5866. *Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.31; N, 7.82. Found: C, 66.84; H, 7.26; N, 7.71.

***p*-Methylbenzylideneethanolamine** had mp 67–69°. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.58; H, 8.02; N, 8.58. Found: C, 73.75; H, 8.06; N, 8.74.

Benzylideneethanolamine had bp 92° (0.7 mm), $n^{23.5}D$ 1.5731 (lit.[4] bp 161–162° (30 mm), $n^{25}D$ 1.5729). Bergmann, Zimkin, and Pinchas[4] showed conclusively that this compound is the Schiff base and not the cyclic derivative.

***p*-Chlorobenzylideneethanolamine** had mp 71–73°. *Anal.* Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; Cl, 19.31; N, 7.63. Found: C, 58.59; H, 5.48; Cl, 19.25; N, 7.57.

***p*-Nitrobenzylideneethanolamine** had mp 82–83° (lit.[4] mp 84.5–85°). The infrared spectra of all of the ethanolamine derivatives were consistent with the Schiff base structure.

The concentrations of the acid solutions employed in the kinetic studies were determined by titration with standardized base. The most concentrated NaCl solution was prepared by weighing out directly the required amount of salt, and the lower concentrations were then obtained by dilution. Dioxane was purified by the method of Fieser[5] and was stored frozen.

Kinetic Measurements. The rates were measured spectrophotometrically at various wavelengths between 250 and 325 mμ with a Zeiss PMQ 11 or Beckman DU spectrophotometer equipped with a Gilford Model 2000 recorder. The oxazolidine, dissolved in di-

(1) For the evidence which has led to this mechanism and the pertinent references see: T. H. Fife and L. K. Jao, *J. Org. Chem.*, 30, 1492 (1965).

(2) Evidence has been presented which would suggest incursion of a mechanism involving solvent participation in the hydrolysis of 2-substituted phenyl-4,4,5,5-tetramethyl-1,3-dioxolanes: T. H. Fife, *J. Amer. Chem. Soc.*, 89, 3228 (1967).

(3) L. H. Goodson and H. Christopher, *ibid.*, 72, 358 (1950).

(4) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. Trav. Chim.*, 71 168 (1952).

(5) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

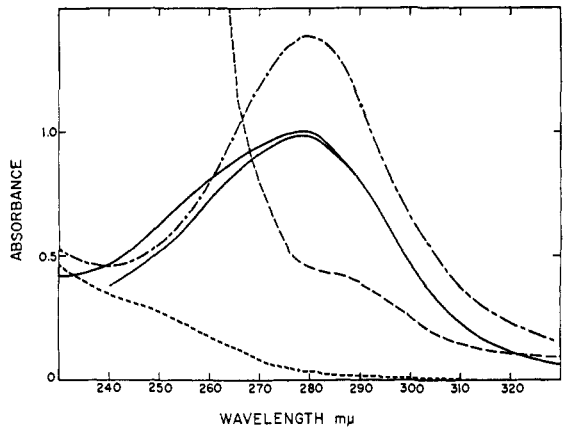


Figure 1. (a) Absorption spectrum of 2-phenyl-3-ethyloxazolidine in dioxane..... (b) Absorption spectrum of the intermediate in the hydrolysis of 2-phenyl-3-ethyloxazolidine in 5.74 *M* HCl ——. The lower line represents a scan begun 3.5 min after addition of starting material to the cuvette with stirring while the upper line represents a scan begun 6 min after addition of starting material (*ca.* nine half-lives). (c) Absorption spectrum of the final product of the reaction (benzaldehyde) – – – –. (d) Absorption spectrum of the Schiff base of benzaldehyde and ethanolamine in 5.74 *M* HCl –·–·–·–. Concentrations of 2-phenyl-3-ethyloxazolidine and benzaldehyde were identical while that of benzylideneethanolamine was slightly less.

oxane, was added to the solution in a thermostated cuvette in the cell compartment of the spectrophotometer by means of a calibrated dropping pipet. One drop was added, and the solution was then stirred vigorously. The rates were generally followed to completion. Pseudo-first-order rate constants (k_{obsd}) were obtained from the slopes of plots of log $[a/(a - x)]$ *vs.* time. Constant temperature (±0.1°) was maintained in the kinetic runs by circulating water from a Haake Model F constant-temperature circulating bath through a Zeiss constant-temperature cell holder or around the cell compartment of the Beckman DU.

In work utilizing 99.8% D_2O as solvent, the glass electrode correction formula of Fife and Bruice[6] was employed in the determination of a_D.

In the determination of activation parameters for hydrolysis of 2-phenyl-3-ethyloxazolidine in 5.74 and 2.37 *M* HCl, points were obtained at four temperatures (12, 19.7, 30, and 40°). The rates were measured in triplicate at each temperature with an average deviation of 2% in the rate constants.

Results

In Table I are given rate constants for the hydrolysis of the series of 2-(substituted phenyl)-3-ethyloxazolidines in moderately concentrated HCl and NaCl solutions where the substrates are completely protonated.[7] In these solutions two different reactions could be monitored for all of the compounds except the *p*-nitro derivative by following the reactions at various wavelengths between 250 and 325 mμ. Thus, for 2-phenyl-3-ethyloxazolidine at acid concentrations greater than 0.1 *M* the absorbance very rapidly increases to a maximum at wavelengths above 280 mμ. This rapid increase in absorbance is then followed by a much slower decrease. Both of these processes are nicely first order with the increase in absorbance taking place 29–72 times faster depending upon the acid concentration. A highly absorbing intermediate is thus being produced in the reaction. It should be noted that the observed rate constant for breakdown of an intermediate in rapid equilibrium with starting material may be smaller than the true rate constant for breakdown since if formation of the intermediate has not been complete it will be partially replenished as hydrolysis takes place. The ultraviolet spectrum at the conclusion of the reaction was identical with that of benzaldehyde. The final product with all of the compounds in the series was shown in the same manner to be the corresponding aldehyde.

Table I. Rate Constants for Hydrolysis of 2-(*para*-Substituted phenyl)-3-ethyloxazolidines in HCl and NaCl Solutions at 30°

Compd[a]	HCl concn, *M*	NaCl, *M*	k_{obsd},[b] min^{-1}	k'_{obsd},[c] min^{-1}
OCH_3	3.57		0.972	0.0321
OCH_3	5.90		0.440	
CH_3	3.57		1.35	0.0601
CH_3	5.90		0.495	
H	1.00		11.42	0.313
H	2.37		4.84	0.166
H	3.57		2.52	0.0854
H	4.77		1.53	0.0376
H	5.74		1.22	0.017
H	5.90		0.949	
Cl	3.57		5.93	0.130
Cl	5.90		1.70	
NO_2	3.57			0.212
H		0.15[d]		0.939
H		3.0[d]	7.74	0.241
H		5.0[d]	2.53	0.105
2-Phenyl-2-methyl-	5.90		2.00	
3-ethyloxazolidine	3.65		5.50	0.00889

[a] *para* substituent. [b] Ring opening. [c] Hydrolysis of the intermediate. [d] In 0.1 *M* HCl.

In 5.74 *M* HCl the intermediate in the hydrolysis of 2-phenyl-3-ethyloxazolidine decomposes at a relatively slow rate so that the reasonably accurate spectrum shown in Figure 1 could be obtained. This spectrum is similar to that of the Schiff base of benzaldehyde and ethanolamine, which would be completely protonated in 5.74 *M* HCl, in that an intense absorption maximum is present at 279 mμ. As the intermediate hydrolyzed this peak decreased in intensity, while at lower wavelengths the absorbance increased to give the characteristic spectrum of benzaldehyde. The ultraviolet spectrum in 5.74 *M* HCl of the intermediate produced in the hydrolysis of each of the N-ethyloxazolidines studied corresponded closely to that of the Schiff base of the appropriately substituted benzaldehyde and ethanolamine. The positions of the absorption maximas for the observed intermediates and the benzylidineethanolamines are: *p*-OCH_3, 324 mμ; *p*-CH_3, 295 mμ (intermediate, 293 mμ); *p*-H, 279 mμ; and *p*-Cl, 291 mμ.

The rate constants for hydrolysis of the substituted benzylideneethanolamines in various acid solutions are reported in Table II. These rate constants are similar in magnitude to those of the intermediates in N-ethyloxazolidine hydrolysis but are generally somewhat smaller.

It is likely that the intermediates in the reactions are the cationic Schiff bases. Ring cleavage must therefore

(6) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

(7) The pK_a values could not be determined because of the great lability of the compounds; however, it has been found that the pK_a values of correspondingly substituted *erythro*-2-(*para*-substituted phenyl 3,4-dimethyl-5-phenyloxazolidines (*p*-CH_3 to NO_2) range from 6.16 to 4.55 while those of the *threo* derivatives range from 5.28 to 3.79: R. W. Cleary, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1964. It is likely that the present series of compounds would have similar values.

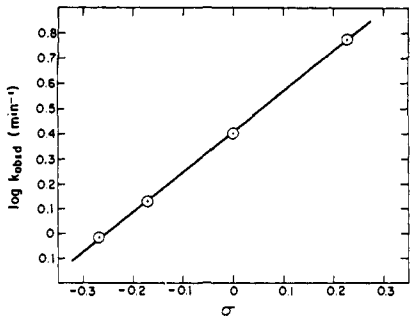


Figure 2. Plot of log k_{obsd} for intermediate formation during the hydrolysis of 2-(*para*-substituted phenyl)-3-ethyloxazolidines in 3.57 *M* HCl at 30° *vs.* σ.

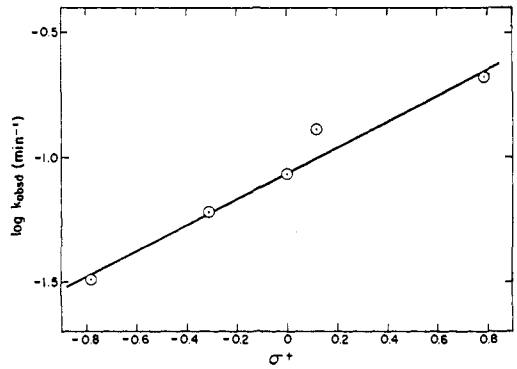


Figure 3. Plot of log k_{obsd} for hydrolysis of the intermediate formed during the hydrolysis of 2-(*para*-substituted phenyl)-3-ethyloxazolidines in 3.57 *M* HCl at 30° *vs.* σ^+.

be taking place between carbon and oxygen. Cleavage of the C–N bond should not lead to an intermediate with absorbancy greater than the corresponding aldehyde. The intensity of absorption is highly dependent on acid concentration, becoming greater as the acid concentration increases when equal amounts of substrate are utilized. The rate of decrease in absorbance at the absorption maximum is identical with the rate of aldehyde formation measured at lower wavelengths.

Table II. Rates of Hydrolysis (k_{obsd} min^{-1}) of *para*-Substituted Benzylideneethanolamines in Various HCl Solutions at 30°

Compd[a]	3.65 *M*	1.0 *M*	0.10 *M*
OCH_3	0.0025	0.0130	0.0849
CH_3	0.0042	0.0305	0.284
H	0.0095	0.0794	0.735
Cl	0.0204	0.189	2.57
NO_2	0.180	2.17	

[a] *para* substituent.

In Figure 2 is presented a plot of log k_{obsd} for formation of the intermediate in 3.57 *M* HCl *vs.* σ, the Hammett substituent constants.[8] A linear relationship is obtained with ρ having the value of +1.6. A plot of log k_{obsd} for decomposition of the intermediate *vs.* σ^+[9] in Figure 3 is linear with a ρ^+ of +0.5, whereas a pronounced downward curvature was found in a plot

(8) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(9) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).

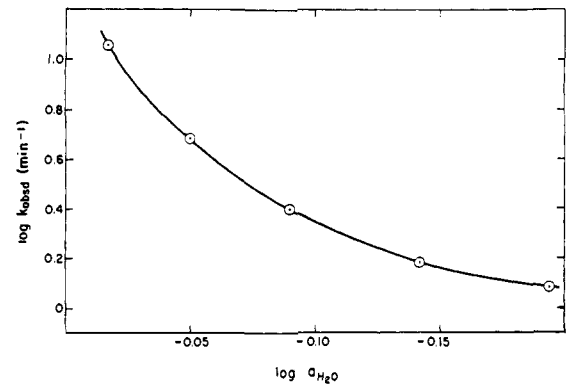


Figure 4. Plot of log k_{obsd} for intermediate formation during the hydrolysis of 2-phenyl-3-ethyloxazolidine in moderately concentrated HCl at 30° *vs.* the logarithms of the activity of water obtained from the data in ref 19.

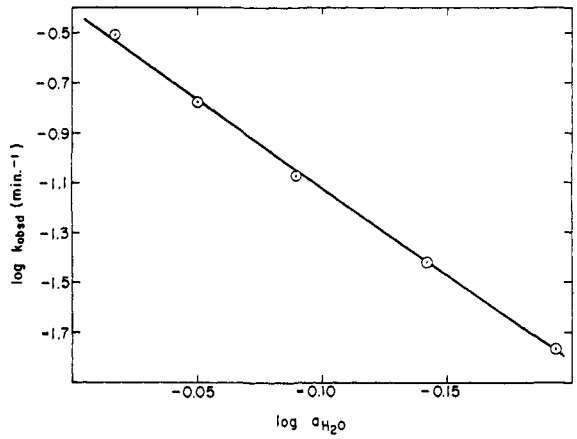


Figure 5. Plot of log k_{obsd} for decomposition of the intermediate formed during the hydrolysis of 2-phenyl-3-ethyloxazolidine in moderately concentrated HCl at 30° *vs.* the logarithms of the activity of water.

using the σ constants. The small value of ρ^+ is in contrast to the large value of +2.17 reported by Cordes and Jencks[10] for hydrolysis of substituted benzylidene-1,1-dimethylethylamines in 0.1 *M* HCl and is in contrast to the magnitude of ρ (+2.0) for hydrolysis of the substituted benzaldehydeethanolamine Schiff bases in 3.65 *M* HCl.

Both formation and decomposition of the intermediate display decreasing rates as the acid concentration increases. In Figure 4 is shown a plot of log k_{obsd} for formation of the intermediate *vs.* the logarithms of the activity of water in these solutions. It can be seen that a curved relationship is obtained. Decomposition of the intermediate, however, gave a reasonably straight line, as shown in Figure 5, with a slope, *w*, of +7.1.

Large rate decreases were also observed for hydrolysis of 2-phenyl-3-ethyloxazolidine in solutions of NaCl as the salt concentration was increased above 1 *M*, keeping HCl concentration constant at 0.1 *M*. The two observed steps of the reaction both showed the negative salt effect.

Activation parameters were obtained for the hydrolysis of 2-phenyl-3-ethyloxazolidine in 5.74 and

(10) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963).

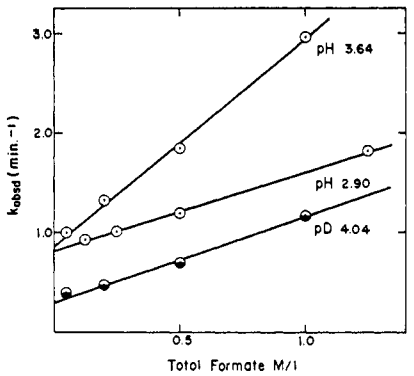


Figure 6. Plots of k_{obsd} for intermediate formation during the hydrolysis of 2-(*p*-methoxyphenyl)-3-ethyloxazolidine at 12° *vs.* the total concentration of formate buffer ($HCOO^-$ + HCOOH) in H_2O ⊙ and D_2O ◒.

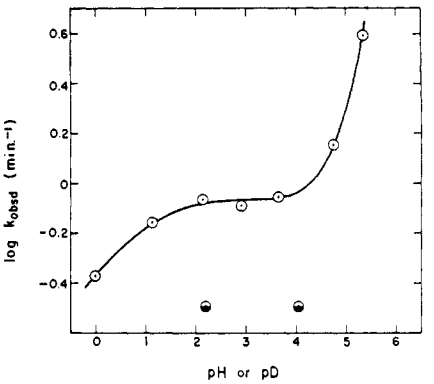


Figure 7. Plot of log k_{obsd} for intermediate formation during the hydrolysis of 2-(*p*-methoxyphenyl)-3-ethyloxazolidine at 12° *vs.* pH ⊙ or pD ◒.

2.37 *M* HCl. The values of ΔH^* and ΔS^* are reported in Table III.

Table III. Activation Parameters for Hydrolysis of 2-Phenyl-3-ethyloxazolidine

HCl concn, *M*	Ring opening ΔH^*,[a] kcal/mol	ΔS^*,[b] eu	Intermediate hydrolysis ΔH^*,[a] kcal/mol	ΔS^*,[b] eu
2.37	15.1	−13.9	18.8	−8.6
5.74	15.4	−15.5	19.8	−9.6

[a] Estimated error is ±1.0 kcal/mol. [b] Calculated at 30°. Rate constants have the units sec^{-1}.

Two steps were also discernable for the hydrolysis of 2-(*p*-methoxyphenyl)-3-ethyloxazolidine at all pH values below pH 5.34 at 12°. At 324 mμ the absorbance increases rapidly to a maximum value and then decreases slowly as was similarly observed in more concentrated acid and salt solutions. The step in which the intermediate is formed (ring opening) was found to proceed more slowly in D_2O than in H_2O (k_{H_2O}/k_{D_2O} = 2.65). A very slight difference in pH and pD in these reactions will not affect the ratio of the rate constants since the reactions are nearly independent of acid concentration in the range studied. These rate constants are reported in Table IV. Formation of the intermediate is strongly catalyzed by buffer. The rate constants for reactions studied in acetate and formate buffers are also reported in Table IV. In Figure 6 are shown plots of k_{obsd} *vs.* the total concentration of formate buffer for reactions at two pH values in water and one pD value in D_2O. The slopes of these plots increase as the pH increases showing the base form to be catalytically active if the reaction is assumed to be hydrolysis of the fully protonated species. The interpretation of these data is complicated by the fact that the pK_a value for 2-(*p*-methoxyphenyl)-3-ethyloxazolidine is unknown, and the possibilities general acid catalysis of neutral species hydrolysis and general bases catalysis of protonated species hydrolysis are kinetically indistinguishable. The second-order rate constant for formate buffer catalysis in water is 2.55 times larger than that in D_2O measured at equal buffer ratios. The pH–rate profile for ring opening is shown in Figure 7. The points at pH values below 2.90 were measured in HCl solutions while at pH 2.90 and above the points were obtained by extrapolation to zero buffer concentration. A pH-independent region is observed from pH 2 to 4. At values above pH 4 the rate increases with increasing pH possibly due to approach to the pK_a with increasing amounts of a more reactive neutral species being present. In alkaline solution (pH 12.0) decomposition to aldehyde takes place readily at 12° (k_{obsd} = 2.38 × 10^{-1} min^{-1}), but formation of an intermediate was not observed.

Formation of an intermediate could not be observed at acid concentrations less than 0.1 *M* with compounds other than the *p*-methoxy and *p*-methyl derivatives. This is most likely due to the intermediate being present at fairly low concentrations, a condition which could result from reduced ratios of the rates of ring opening and Schiff base hydrolysis. A reaction in which aldehyde is formed, characterized by an increase in ab-

Table IV. Rate Constants for Ring Opening and Hydrolysis of the Intermediate from 2-(*p*-Methoxyphenyl)-3-ethyloxazolidine at 12°

pH (H_2O)	pD (D_2O)	k_{obsd},[a] min^{-1}	l. mol^{-1} min^{-1} k_{HCOO^-}[a]	$k_{CH_3COO^-}$[a]	l. mol^{-1} min^{-1} k'_{HCOO^-}[b]	$k'_{CH_3COO^-}$[b]
0[c]		0.427				
1.14		0.679				
2.13		0.852				
2.90		0.810[d]	3.97		0.305	
3.64		0.880[d]	4.16			
4.75		1.42[d]		13.8		1.01
5.34		3.90[d]		13.9		1.10
	2.20	0.320				
	4.04	0.320[d]				

[a] Ring opening. [b] Hydrolysis of the intermediate. [c] 1.00 *M* HCl. [d] Extrapolated to zero buffer concentration, μ = 0.5 *M*.

Table V. Rate Constants (k_{obsd} min^{-1}) for Hydrolysis of 2-(Substituted phenyl)-3-ethyloxazolidines at μ = 0.25 *M* and 30°

Compd[a]	pH 1.12	pH 2.13	pH 3.04	pD 2.30 (D_2O)
p-OCH_3	0.600	0.674	0.714	
p-CH_3		0.901	0.981	
H	0.939	0.933	1.01	0.425
p-Cl		1.19	1.28	
m-Cl		1.26		
p-NO_2		1.58	1.81	

[a] Substituent.

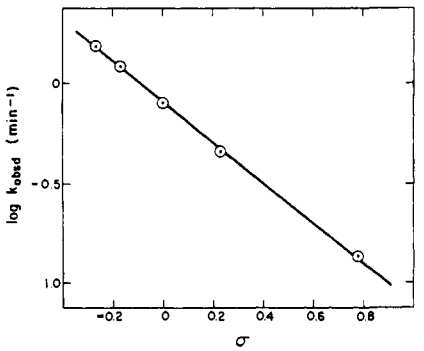


Figure 8. Plot of log k_{obsd} for aldehyde formation from 2-(substituted phenyl)-3-ethyloxazolidines in 0.01 M NaOH at 30° *vs.* σ.

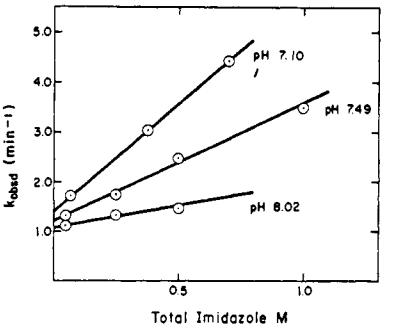


Figure 9. Plot of k_{obsd} for aldehyde formation from 2-phenyl-3-ethyloxazolidine *vs.* the total concentration of imidazole buffer (Im + ImH$^+$).

sorbance at wavelengths from 255 to 290 mμ, was observed for all compounds. At the conclusion of this reaction the spectrum of the solution was that of the product aldehyde. Rate constants for aldehyde formation in these reactions are given in Table V.

Rate constants for aldehyde formation with the various compounds in alkaline solution are given in Table VI. Again an intermediate could not be observed. Infinity points were reasonably stable although that for the *p*-NO_2 derivative in 0.01 M NaOH did decrease slightly at times greater than ten half-lives. The observed rate constants are nearly independent of pH. In Figure 8 is presented a plot of the logarithms of the rate constants for hydrolysis in 0.01 M NaOH *vs.* σ. A straight line relationship is observed with a ρ of −1.1.

Table VI. Rate Constants (k_{obsd} min^{-1}) for Hydrolysis of 2-(*para*-Substituted phenyl)-3-ethyloxazolidines in Alkaline Solution at 30°

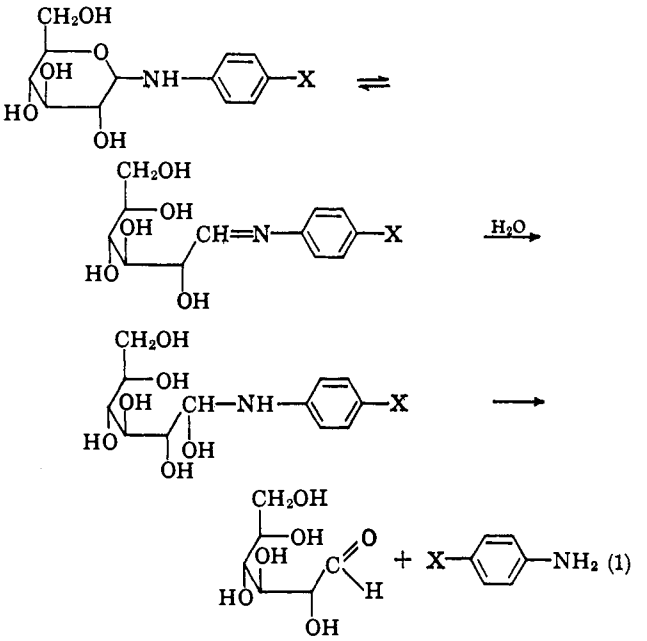
Compd[a]	pH 7.49	pH 10.07	pH 10.76	pH 12.06	pD 12.55 (D_2O)
OCH_3			1.38	1.54	
CH_3			1.16	1.22	
H	1.18[b]	0.851	0.846	0.806	0.431
Cl			0.515	0.461	
NO_2	0.312[b]		0.138	0.136	

[a] *para* substituent. [b] Rate constants obtained by extrapolation to zero imidazole concentration.

Aldehyde formation was found to be subject to a large buffer catalysis, imidazole buffer acting as an efficient catalyst for the hydrolysis of both 2-phenyl- and 2-(*p*-nitrophenyl)-3-ethyloxazolidine. In Figure 9 are shown plots of k_{obsd} *vs.* the total concentration of imidazole buffer (Im + ImH$^+$) for hydrolysis of 2-phenyl-3-ethyloxazolidine. The slopes increase as the pH decreases, showing kinetic dependence on the acid species. The values of k_{ImH^+} were 8.09 l. mol^{-1} min^{-1} for 2-phenyl-3-ethoxyoxazolidine and 1.36 l. mol^{-1} min^{-1} for the *p*-NO_2 derivative. The rate constants found by extrapolation to zero buffer concentration showed that spontaneous hydrolysis was much less rapid for the *p*-NO_2 derivative (k_H/k_{NO_2} = 3.8 at pH 7.49). At pH 10.07, 1.0 M imidazole had no effect on the rates of hydrolysis of 2-phenyl- and 2-(*p*-nitrophenyl)-3-ethyloxazolidine. At that pH the imidazole would be almost completely in the free base form (pK_a = 7.10 at 30°).

Discussion

In recent studies of the mechanism of hydrolysis of various glucosylamines, a Schiff base intermediate has been postulated.[11,12] Capon and Connett[11] prefer the scheme shown in eq 1 in which the ring opens in a fast

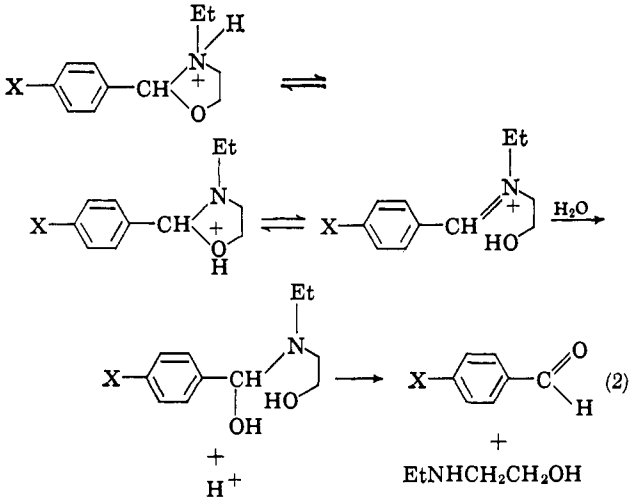


step followed by rate-determining hydrolysis of the Schiff base. Evidence thought to support this scheme included the D_2O solvent isotope effect (k_{D_2O}/k_{H_2O} = 1.05 at low acidity and 0.45 at high acidity) and an observed general acid catalysis.[11] The 2-(substituted phenyl)-3-ethyloxazolidines offer a great advantage for study since in moderately concentrated acid the rate of formation of an intermediate can be measured as well as its rate of hydrolysis. The intermediate being formed in the hydrolysis of the oxazolidines is very likely a cationic Schiff base. The protonated Schiff bases of substituted benzaldehydes and ethanolamine can be considered models for the cationic Schiff bases that would be formed from the oxazolidines. The near identity of the ultraviolet spectrum of each of the observed intermediates with that of the corresponding protonated Schiff base provides strong evidence that the intermediate in the reaction is indeed this type of compound. Cationic Schiff bases have been postulated

(11) B. Capon and B. E. Connett, *J. Chem. Soc.*, 4497 (1965).
(12) H. Simon and D. Palm, *Chem. Ber.*, **98**, 433 (1965).

previously to be intermediates in the reactions of morpholine and proline with pyridoxal phosphate.[13]

A scheme similar to eq 1, involving unimolecular ring opening followed by cationic Schiff base hydrolysis, is shown for oxazolidine hydrolysis in eq 2. Such

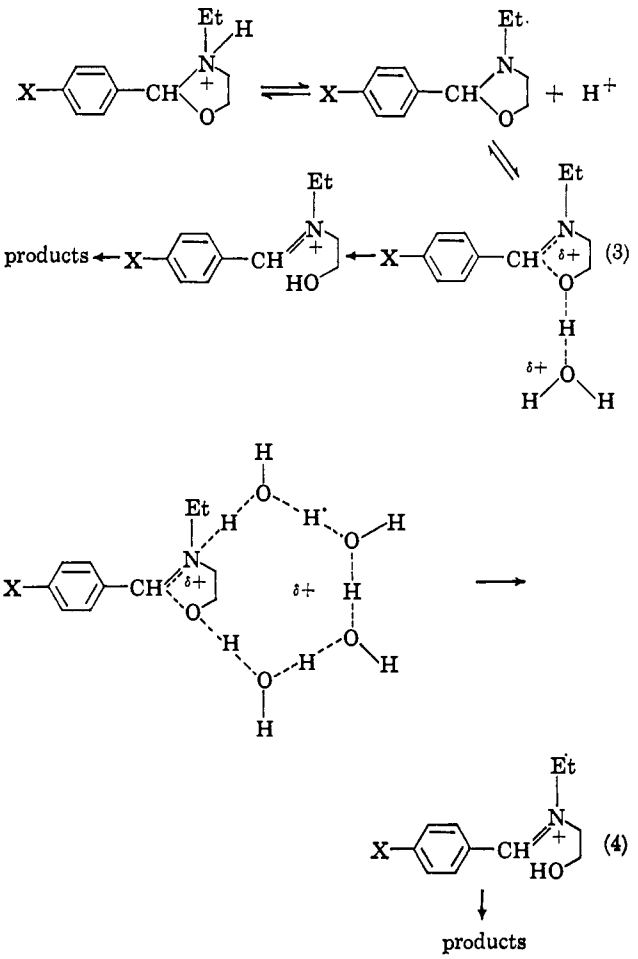


(2)

a unimolecular ring opening is not in accord with several pieces of evidence: (a) intermediate formation is much slower in D_2O than in H_2O for 2-(*p*-methoxyphenyl)-3-ethyloxazolidine (k_{H_2O}/k_{D_2O} = 2.65); (b) general catalysis is observed for this reaction; (c) increasing concentrations of salt and acid produce large rate-decreasing effects; and (d) negative values were found for ΔS^*. Positive entropies of activation have been observed in numerous instances for reactions proceeding with rate-determining unimolecular decomposition of a protonated substrate while reactions involving attack of solvent on the protonated substrate normally have negative ΔS^* values, usually in excess of -15 eu.[14] The values observed in the ring opening, -15.5 eu in 5.74 *M* HCl and -13.9 eu in 2.37 *M* HCl, while not highly negative are still more nearly in accord with a reaction involving solvent participation than with a unimolecular reaction.

Several other reactions have been found to exhibit decreased rates in moderately concentrated acid where complete protonation of the substrate has occurred, examples being the hydrolysis reactions of amides,[15] N-acylimidazoles,[16] Schiff bases,[17] and ethylbenzimidates.[18] These reactions undoubtedly involve participation by solvent in the critical transition state. The rate decreases have in certain cases been partially explained by the decrease in water activity as acid concentration is increased[19] or by a possible change in rate-determining step.[16b] Curved *w* plots[19] such as observed in the ring opening of 2-phenyl-3-ethyloxazolidine (Figure 4) have been noted previously in the hydrolysis of N-acylimidazoles[16] and may be characteristic of reactions where several water molecules are involved in the transition state. The actual number of water molecules involved in oxazolidine hydrolysis cannot be specified with certainty, but the high initial slope of the *w* plot would indicate that this number is large.

It seems certain that solvent must be involved in the ring-opening reaction although the actual mode of participation is not clear. A possible mechanism might involve partially rate-determining protonation of oxygen in concert with C–O bond breaking, assuming the N-protonated species to be unreactive (eq 3). Since only minute amounts of unprotonated species would be present at high acidity, very large second-order rate constants would be required for such a process (of the order of 10^5–10^6 l. mol^{-1} min^{-1} for the unsubstituted derivative assuming a reasonable pK_a of $\sim$5).[7] Proton transfer might also take place in a concerted manner (eq 4) through a chain of hydrogen-bonded water



(3)

(4)

molecules. This mechanism is similar to that proposed by Bunton and Shiner for mutarotation of sugars.[20] The large positive ρ value (+1.6) might result from such mechanisms since proton removal from nitrogen would be facilitated by electron withdrawal. A positive contribution to ρ would also result if the charge on carbon is smaller in the transition state than in the ground state. Proton transfer to oxygen from hydronium ion (or a water molecule) and departure of the

(13) E. H. Cordes and W. P. Jencks, *Biochemistry*, **1**, 773 (1962).
(14) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Amer. Chem. Soc.*, **79**, 2362 (1957); L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(15) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000, 2009 (1957); D. Rosenthal and T. I. Taylor, *J. Amer. Chem. Soc.*, **79**, 2684 (1957); J. A. Leisten, *J. Chem. Soc.*, 765 (1959); R. H. De Wolfe, *J. Amer. Chem. Soc.*, **82**, 1585 (1960).
(16) (a) J. A. Fee and T. H. Fife, *J. Phys. Chem.*, 70, 3268 (1966); (b) S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 232 (1962).
(17) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962).
(18) R. H. De Wolfe and F. B. Augustine, *J. Org. Chem.*, 30, 699 (1965).
(19) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4958, 4973, 4978 (1961).
(20) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 3214 (1961).

leaving group would be inhibited by electron withdrawal. The observed ρ must then represent a compromise between these opposing effects. The ρ value is, however, difficult to interpret in a straightforward manner since it is dependent upon the magnitude of the rate-decreasing effect of increased acid concentration and upon the position of the pH–rate maximum for each of the compounds. Mechanism 3 predicts general acid catalysis of neutral species hydrolysis, while a general base catalyzed hydrolysis of the protonated species involving a concerted type of mechanism similar to (4) could take place with partial abstraction of the proton from nitrogen by the catalyzing base. These possibilities are kinetically equivalent. The observed buffer catalysis does not, therefore, allow distinction between these mechanisms.

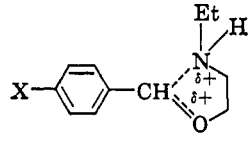
Mechanisms involving solvent-assisted nucleophilic attack of water on the protonated oxazolidine to give a carbinolamine intermediate, which could dehydrate in concentrated acid to a cationic Schiff base, appear unlikely[21] since it was observed that substitution of a methyl group for the hydrogen at position 2 in 2-phenyl-2-methyl-3-ethyloxazolidine produces a rate acceleration. It would be expected that nucleophilic attack would be strongly retarded by such substitution, whereas a direct ring opening to a Schiff base might be facilitated as is the hydrolysis of the corresponding diethyl acetals and ketals.[22]

The formation of aldehyde at high pH values where the unprotonated oxazolidine is the predominant species is nearly pH independent. This can be reasonably explained by mechanisms involving: (a) water-catalyzed or uncatalyzed ring opening that is rate determining; (b) preequilibrium formation of Schiff base in a hydronium ion requiring reaction followed by attack of hydroxide ion on the Schiff base;[23] or (c) attack of hydroxide ion on the protonated oxazolidine, which appears less likely in view of the evidence favoring mechanism 3–4 for ring opening at high acidity.

The logarithms of the rate constants for hydrolysis in 0.01 *M* NaOH give a linear relationship with σ with $\rho = -1.1$. Jencks and Cordes[10] obtained a ρ^+ value of -0.21 for hydrolysis of benzylidine-1,1-dimethylethylamines at pH 9–14 where the reaction involves protonation of the Schiff base followed by hydroxide ion attack, and a ρ^+ value of $+1.26$ from a plot of the logarithms of the second-order rate constants for hydroxide ion catalyzed hydrolysis of the protonated Schiff bases *vs.* σ^+. Hydroxide ion catalyzed hydrolysis of a cationic Schiff base would, of course, resemble that of a completely protonated Schiff base, so a highly positive value of ρ^+ would be expected for that step. The linear relationship with σ and the negative value of ρ, therefore, indicate that substituent effects on the ring-opening step are of great influence on the observed value of ρ, although ring opening is not necessarily rate determining. Electron withdrawal must be hindering the ring-opening step by making protonation and bond breaking more difficult. This effect is in contrast to the facilitation provided by electron withdrawal at high acidity where protonation is nearly complete.

Although no imidazole catalysis was observed for oxazolidine hydrolysis at high pH (10.07), general acid catalysis by imidazole buffers was found at lower pH values. The rate constants found by extrapolation to zero buffer concentration were of greater magnitude for 2-phenyl-3-ethyloxazolidine than for the p-NO_2 derivative, so at pH 7.49 ρ is still negative as in alkaline solution. General acid catalysis of cationic Schiff base hydrolysis would not be expected since the alkyl group on nitrogen produces the same effect as a proton. General base catalysis of that step might be anticipated, however, as observed for the p-OCH_3 derivative at lower pH (Table IV). The observed general acid catalysis, therefore, is either catalysis of ring opening or general base catalyzed hydrolysis of the intermediate formed in a hydronium ion catalyzed ring-opening step. The lack of general base catalysis at pH 10.07 would be consistent with the suggestion of a general acid catalyzed ring opening, but this is not unambiguous evidence since at high pH general bases might not be able to compete with the high concentrations of hydroxide ion.

One question of interest that arises from the present work concerns the reasons for a difference in the mechanism of hydrolysis for oxazolidines as compared to that for the corresponding acetals (1,3-dioxolanes) which hydrolyze by an A1 mechanism.[1] If a direct ring opening to a cationic Schiff base is taking place as in eq 3–4 then the factor giving rise to the facility of the reaction can best be ascribed to the relative ease of accommodation of the positive charge on nitrogen. It might be expected that a significant percentage of C–N bond cleavage to a carbonium ion intermediate would take place, as in eq 5, since a protonated amine



(5)

is a good leaving group and the carbonium ion is highly stabilized. It is clear, however, that the predominant reaction in acid solution involves C–O cleavage, and this is very likely due to the relative stabilities of the intermediates. The more stable the product of the rate-determining step, then by the Hammond principle[24] the closer the transition state will resemble the ground state. In the case of oxazolidine hydrolysis proton transfer has become partially rate determining. The mechanism of hydrolysis of ortho esters is currently thought to involve rate-determining protonation of the substrate by hydronium ion in concert with C–O bond cleavage.[25] The change in mechanism from that found for acetals and ketals, involving preequilibrium protonation, is presumably due to the fact that ortho esters are much weaker bases.[25] A mechanism such as expressed in eq 4, involving protonation of oxygen for the substrate also partially protonated at nitrogen, would allow a similar argument to be made for oxazolidine

(21) The formation and hydrolysis of Schiff bases and related carbonyl derivatives has been discussed in detail: W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 63 (1964).

(22) T. H. Fife and L. Hagopian, *J. Org. Chem.*, 31, 1772 (1966). The rates of hydrolysis of 2-phenyl-2-alkyl-1,3-dioxolanes are slower, however, than that of 2-phenyl-1,3-dioxolane.

(23) The hydrolysis of benzylidine-1,1-dimethylethylamines at high pH takes place with attack of hydroxide ion on the protonated Schiff base.[10]

(24) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).

(25) C. A. Bunton and R. H. De Wolfe, *J. Org. Chem.*, 30, 1371 (1965).

hydrolysis since protonation of nitrogen would greatly reduce the basicity of oxygen.

It can be definitely concluded that solvent is participating in the ring-opening step and that this step is subject to general catalysis. It would seem likely that this must also be the case in ring opening of the analogous glucosylamines although the different steric and electronic factors makes such generalization difficult.

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Solvolysis of Bicyclo[2.2.0]hexane-1-methyl *p*-Nitrobenzoate[1a]

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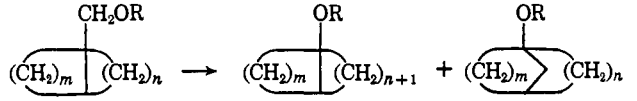
Abstract: Bicyclo[2.2.0]hexane-1-methanol (**10**) was synthesized in a five-step reaction sequence from the Diels–Alder adduct of 5,5-dimethoxytetrachlorocyclopentadiene and ethylene *via* 1,4-dichloro-7,7-dimethoxybicyclo[2.2.1]heptane (**5**), the related 7-ketone **6**, 4-chlorobicyclo[2.2.0]hexane-1-carboxylic acid (**7**), and 4-chlorobicyclo[2.2.0]hexane-1-methanol (**9**). The *p*-nitrobenzoate ester of **10** underwent solvolysis in 60% aqueous acetone at 99.5 and 116.8° to yield 81% of 1-norbornyl *p*-nitrobenzoate (**13**) and 19% 1-norbornanol (**14**). The rate of the reaction is 7×10^6 faster than the extrapolated rate for the corresponding neopentyl derivative. A correlation between rate and strain release is presented as evidence for anchimeric assistance in this type of rearrangement.

Recently the mechanism of the solvolytic reaction of neopentyl-type systems has been analyzed in detail and it has been concluded that in systems where there is little relief of strain by rearrangement the solvolysis proceeds through discrete primary cation ion-pair intermediates and is not anchimerically assisted. In addition, it has been suggested that a mechanism involving participation might be responsible for the enhanced rates observed in some neopentyl-type systems in which substantial strain relief is possible through rearrangement.[2] A series of compounds which appear to encompass both categories are the bicyclo[*m.n.*0]alkane-1-methanols (**1**) since it has been found that as *m* and *n* change from 6,6 to 6,5 to 5,5 the rates of solvolysis at 100° of the *p*-toluenesulfonate esters are 4, 150, and 1000 times, respectively, that of the simple neopentyl derivatives.[3-6] Furthermore, as the rate increases, the type of solvolytic product changes from



1 **2** **3**

2 to **3**. Thus, it continues to be of interest to determine what effects conformation, ring size, and strain have on the course and the rate of neopentyl-type rearrangements.

Bicyclo[2.2.0]hexane-1-methanol (**10**) is of particular interest since it has the highest strain energy of any of the bicyclo[*m.n.*0]alkane-1-methanol systems not containing a cyclopropyl ring; systems containing the latter type of ring system introduce complicating factors due to the unique electronic properties of this ring.[7] The recent preparation of *cis*-4-chlorobicyclo[2.2.0]hexane-1-carboxylic acid[8] has made this interesting ring system available. The acid has been converted to the primary alcohol **10** and the solvolysis of the *p*-nitrobenzoate ester studied.

Synthesis

The Diels–Alder adduct **4** of 5,5-dimethoxytetrachlorocyclopentadiene and ethylene was catalytically hydrogenated to 1,4-dichloro-7,7-dimethoxybicyclo[2.2.1]heptane (**5**). Acid treatment of the ketal **5** gave 1,4-dichlorobicyclo[2.2.1]heptan-7-one (**6**). The chloro ketone **6** reacted readily at 0° with powdered sodium hydroxide in tetrahydrofuran to give *cis*-4-chlorobicyclo[2.2.0]hexane-1-carboxylic acid (**7**). Instability of the Favorskii rearrangement product **7** to the reaction conditions usually used for this type of chloro ketone necessitated the use of milder conditions. This acid **7** was esterified with diazomethane and the ester **8** reduced with lithium aluminum hydride to yield the chlorocarbinol **9**. When large excess of hydride was used in the reduction, loss of the chlorine atom and rearrangement of the nucleus to yield **11** occurred to the extent of 30%. Rearrangement of **9** to **11** probably comes about through ionization (possibly Lewis acid assisted) of the chlorine of **9** alkoxide; a similar rearrangement has been observed in the reaction of **9** with aqueous silver ion.[9] Chlorocarbinol **9** upon reduction with

(1) (a) This work was supported in part by Grant GP-3890, National Science Foundation (to W. G. Dauben), and Grant GM-12731, U. S. Public Health Service, and donors of the Petroleum Research Fund, administered by the American Chemical Society (PRE 2191-A1,4) (to K. V. Scherer). (b) National Institutes of Health Predoctoral Fellow, 1966–1967.

(2) J. E. Nordlander, S. P. Jindal, P. von R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).

(3) W. G. Dauben and J. B. Rogan, *ibid.*, **79**, 5002 (1957).

(4) F. T. Bond, Ph.D. Thesis, University of California.

(5) R. A. Flath, Ph.D. Thesis, University of California.

(6) W. G. Dauben, *Bull. Soc. Chim. France*, 1697 (1964).

(7) With rings of three carbon atoms (*m* and/or *n* = 1), the rate of reaction is very rapid and fragmentation is the major reaction pathway. See: (a) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connar, P. Schertler, and J. Lavanish, *Tetrahedron*, 21, 2749 (1965); (b) W. D. Closson and G. T. Kwiatkowski, *ibid.*, **21**, 2779 (1965); (c) W. G. Dauben and J. Wiseman, *J. Amer. Chem. Soc.*, **89**, 3545 (1967).

(8) K. V. Scherer, Jr., *Tetrahedron Letters*, 5685 (1966).