On removal of the fatty acid by alkali, ring closure could take place with the formation of plasmalogen. From the fact that no migration of phosphoric acid occurs during the treatment of the native acetal phosphatide with alkali[17] it can be deduced that the aldehyde is attached to the β-position. An acetal phosphatide possessing the proposed structure I would not be expected to give rise to the formation of an acid-soluble phosphate ester in the plasmal reaction, unless it has been pretreated with alkali. This is precisely the behavior observed by Schmidt, *et al.*, for the native acetal phosphatide.

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Pigman and Isbell (W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 189 (1937)). See also W. W. Pigman and R. M. Goepp, "Chemistry of the Carbohydrates," Academic Press, Inc., New York, N. Y., 1948, pp. 158-159.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BUCKNELL UNIVERSITY, AND
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On Cyclic Intermediates in Substitution Reactions. III. The Alkaline Hydrolysis of ε-Bromocaproic and ζ-Bromoenanthic Acids

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The rates of aqueous decomposition have been determined for the sodium salts of ε-bromocaproic acid and ζ-bromoenanthic acid. It has been established that (1) the rates of decomposition, as measured by the release of bromide ion, are of the first order with respect to the ion of the haloacid; (2) the entropies of activation are negative and decrease markedly in the order $\epsilon > \zeta$; (3) the heats of activation decrease in the order $\epsilon > \zeta$. These results are discussed in terms of mechanisms involving simple hydrolysis and a cyclic intermediate.

In part I[2] of this series it was shown that in the alkaline hydrolysis of some aliphatic α-, β- and γ-bromoacids, the reactivities increased in the order $\alpha < \beta <<< \gamma$ and that the entropies of activation were positive (about 10 e.u.). The results suggested that in nucleophilic displacement involving intermediate formation of 3-, 4- and 5-membered rings the rate of the displacement process is governed largely by the heat of activation which increases markedly with the strain attending ring formation.

All the bromoacids studied in this investigation involved bromine substitution on the α-, β- or γ-carbons. For the sake of completeness it seemed desirable to determine the behavior of some bromoacids where the carboxylate ion was further removed from the seat of substitution. The present paper reports a study of the hydrolysis of sodium ε-bromocaproate and sodium ζ-bromoenanthate in solutions containing sodium bicarbonate.

Experimental

ε-Bromocaproic Acid.—This acid was prepared according to the procedure of Heine and Jones.[3] The acid was recrystallized from petroleum ether, m.p. 32.5°.

Anal. Calcd. for $C_6H_{11}O_2Br$: Br, 40.9. Found: Br, 40.3.

ζ-Bromoenthanic Acid.—A solution of 78 g. (1.2 moles) of potassium cyanide in 160 ml. of water is added slowly and with stirring to a solution of 244 g. (1.0 mole) of hexamethylene dibromide in 650 ml. of 95% ethanol and the mixture is refluxed for 15 hours. The alcohol (500 ml.) is removed by distillation and the residue is extracted with three 100-ml. portions of benzene. The benzene solutions are combined and washed with 50 ml. of 1 *N* NaOH and then with 50 ml. of water. The benzene is removed by distillation. The residue is vacuum distilled to yield 152 g. of unreacted hexamethylene dibromide boiling at 113–128° (10 mm.), 66 g. of crude ω-bromoenanthonitrile boiling at 129–140° (10 mm.), and 26 g. of crude hexamethylene dicyanide boiling at 140–168° (10 mm.).

Hydrolysis of the crude bromonitrile is effected by refluxing with 48% hydrobromic acid using a twofold molar excess

TABLE I

RATES OF AQUEOUS DECOMPOSITION OF ε-BROMOCAPROATE AND ζ-BROMOENANTHIC ACIDS IN 0.25 *M* SODIUM BICARBONATE

Time, min.	Vol. of 0.05 *N* $AgNO_3$, ml.	10^3k_1 (min.$^{-1}$)	Time, min.	Vol. of 0.05 *N* $AgNO_3$, ml.	10^3k_1 (min.$^{-1}$)
Sodium ε-bromocaproate, $t = 50.00°$			Sodium ζ-bromoenanthate, $t = 70.10°$		
61.75	1.71	1.38	51.5	1.09	4.89
106.3	2.54	1.38	102.5	1.91	4.83
173.1	3.71	1.40	164.3	2.70	4.86
269.6	5.20	1.39	218.6	3.21	4.85
309.6	5.73	1.38	269.5	3.59	4.87
357.8	6.40	1.39	347.6	4.00	4.86
∞	15.61	Mean 1.39	∞	4.90	Mean 4.86

TABLE II

RATE CONSTANTS FOR THE FIRST-ORDER DECOMPOSITION OF ε- AND ζ-BROMOACIDS IN 0.25 *M* SODIUM BICARBONATE

Temp., °C.	10^3k_1 (min.$^{-1}$)	Mean	Temp., °C.	10^3k_1 (min.$^{-1}$)	Mean
ε-Bromocaproic acid			ζ-Bromoenanthic acid		
50.00	1.41	1.40	59.80	1.79	1.78
	1.39			1.79	
	1.44			1.75	
	1.38			1.79	
	1.39		70.10	4.86	4.85
62.72	6.41	6.39		4.86	
	6.38			4.84	
	6.38			4.84	
70.00	13.2	13.2	79.90	12.0	12.1
	13.3			11.9	
	13.2			12.2	
				12.2	

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[1] Deceased, October 17, 1952.

[2] J. F. Lane and H. W. Heine, THIS JOURNAL, **73**, 1348 (1951).

[3] H. W. Heine and H. Jones, *ibid.*, **73**, 1361 (1951).

of the acid. The reaction mixture is extracted with ether and the ethereal extract dried with sodium sulfate. The solvent is removed and the ζ-bromoenanthic acid is distilled at 165–168° (11 mm.). The crude product was recrystallized several times from pentane to yield 17.8 g. or 22% yield of ζ-bromoenanthic acid, m.p. 29–30°.

Anal. Calcd. for $C_7H_{13}O_2Br$: Br, 38.2. Found: Br, 37.9.

Method of Rate Measurement.—The experimental method previously described[2] for measuring the release of bromide ion was followed. The initial concentration of bromoacid was 0.04 *M* in all but a few measurements which were run at a concentration of 0.1 *M*. The initial concentration of sodium bicarbonate was 0.25 *M*. Typical rate data for the bromoacids are given in Table I. Table II summarizes the complete data on first-order rate constants for both of the acids studied.

Discussion of the Results

By applying to the data of Table I the interpretation of the transition state theory[4] values for the entropy and the heat of activation may be calculated. Values of these "thermodynamic" quantities for ε-bromocaproate and ζ-bromoenanthate and also the previously investigated α-bromopropionate, α-bromocaproate, β-bromopropionate, β-bromocaproate and γ-bromovalerate ions are given in Table III.

TABLE III

"THERMODYNAMIC" QUANTITIES OF ACTIVATION, TOGETHER WITH ESTIMATED RATES OF DECOMPOSITION AT 25° FOR SOME BROMOACIDS IN 0.25 *M* SODIUM BICARBONATE

Acid	$\Delta H^{\ddagger}$, kcal.	$\Delta S^{\ddagger}$, e.u.	k_1 (min.$^{-1}$)
α-Bromopropionic	29.7	11	2.5×10^{-5}
α-Bromocaproic	29.2	10	3.3×10^{-5}
β-Bromopropionic	28.7	13	2.1×10^{-4}
β-Bromocaproic	27.1	12	2.1×10^{-3}
γ-Bromovalerate[5]	22.2	11	0.33
ε-Bromocaproic	25.2	−2	1.0×10^{-4}
ζ-Bromoenanthate	22.2	−13	2.6×10^{-5}

The high positive entropy values for α-bromopropionate, α-bromocaproate, β-bromopropionate, β-bromocaproate and γ-bromovalerate indicate an increase in the freedom of the system as a whole when the reactant passes into the transition state, and as previously noted[2] are most probably due to a freeing of water molecules which were oriented stiffly or frozen around the carboxylate ion. Such "melting" can only occur if the carboxylate ion itself effects substitution with attendant formation of a lactone.

The low value of entropy of activation for the ε-bromocaproate ion suggests that here ring formation may account for only a portion of the total substitution process, the remainder proceeding through a simple hydrolysis. The very low value for the entropy of ζ-bromoenanthoate ion is, in our opinion, best interpreted as due to just hydrolysis. In this event the carboxylate ion would not be involved directly in the formation of the transition state and thus no "melting off" of water molecules from it would take place. This is in harmony with the observation of Braun[6] that no lactone was formed when ζ-bromoenanthic acid was decomposed with boiling water.[7]

It is of interest in this connection to compare the heats and entropies involved in these processes with the corresponding quantities (22.5 kcal., −15 e.u.) observed by Hughes and Ingold[8] for the hydrolysis of isopropyl bromide in 60% ethanol. In this system, the low entropy is to be associated with the freezing of water molecules on the transition state, a process which lowers the heat of activation to a value comparable to that found in the most rapid process (decomposition of γ-bromovalerate) observed here.

Taken as a whole, the results suggest that in substitution processes involving the formation of 3-, 4- and 5-membered cyclic intermediates, variations in the size of the ring formed and in the total number of carbon atoms in the molecule produce negligible variations in the entropies of activation. As a result, speeds of such processes are governed almost entirely by the strain attending ring formation. When the distance between the bromine and the carboxylate ion is increased to five or six methylene groups, it becomes difficult for the carboxylate ion to participate in the formation of the transition state and simple hydrolysis accounts for most of the substitution process.

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[4] H. Eyring and M. Polanyi, *Z. physik. Chem.*, **B12**, 279 (1931).

[5] The previous value of $T\Delta S^{\ddagger}$ for γ-bromovalerate was reported erroneously and should be 3.0.

[6] J. V. Braun, *Ber.*, **39**, 4362 (1906).

[7] The kinetic evidence also allows an alternative viewpoint of the substitution process, for even if lactone formation occurs, the rate could reasonably be expected to have a low probability factor since the carboxylate group will only occasionally be near the back side of the carbon-bearing bromine. The probability could be so low as to compensate for the freeing of frozen solvent molecules.

[8] E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 252 (1935).