is used. The values of r and s obtained for the series at 25° which includes the pK_{a_1} of malonic acid (correlated by a statistical factor of 0.5) are 0.989 and 0.131, respectively, slightly worse than those given in Table III for the series omitting this point. The value of σ_I calculated for the CO_2H group on the basis of series 1f is 0.39. This value seems somewhat high. The use of eq. 3 gives a value of 0.33. The carbomethoxy and carbethoxy groups have σ_I values of 0.34 and 0.34, respectively (Table IV). Presumably, the value of σ_I will be about the same as the values for CO_2Me and CO_2Et.

Effect of Temperature on the Reaction Constant.—The values of ρ obtained for series 1a–k permit a test of the relationship

$$\rho = \frac{m}{T} + c \qquad (6)$$

which has been proposed by a number of authors, and most recently by Hepler.[5] Correlation of the ρ values for series 1a–k with eq. 6 gives very poor results (r = 0.579, t = 2.129, n = 11). The ρ values seem by inspection more likely to fit a parabolic relationship. This is in accord with the observation that ionization constants of aliphatic carboxylic acids fit the parabolic equation

$$\log K = \log K_m - p(T - T_m)^2 \qquad (7)$$

where K_m is the maximum value of K, occurring at the maximum temperature T_m.[6] Thus, for these series of ionization constants, eq. 6 is not obeyed.

(5) L. Hepler, *J. Am. Chem. Soc.*, **85**, 3089 (1963).
(6) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 69.

Solvolysis of Substituted γ-Butyrolactones and δ-Valerolactones

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Methyl substitution of γ-butyrolactone results in a reduction of the equilibrium constants for hydrolysis. This is due to a combination of the enhancement of the rate of ring closure and reduction in the ease of ring opening by substitution, the first factor being the more important. The results for the δ-valerolactones confirm these findings.

A previous publication[2] reported the influence of methyl substitution on the rate of saponification of γ-butyrolactone in 92.3% ethanol–water. Shechter and co-workers[3] have carried out similar studies in 50% dimethoxyethane–water and also have measured the basic hydrolysis of several δ-valerolactones. This paper reports measurements of the equilibrium constants of substituted γ-butyro- and δ-valerolactones in acid solution. The values of the rate constants of acid-catalyzed hydrolysis of γ-butyrolactone and γ-methylbutyrolactone (where the equilibrium constants were sufficiently large) and of the δ-valerolactones were determined also (see Tables I and II).

TABLE I

HYDROLYSIS OF BUTYROLACTONES[a]

Butyrolactone	25°, l. mole^{-1} min.$^{-1}$ $K_H \times 10^2$	25°, l. mole^{-1} min.$^{-1}$ $k_H \times 10^2$	0°, l. mole^{-1} min.$^{-1}$ $K_H \times 10^2$	0°, l. mole^{-1} min.$^{-1}$ $k_H \times 10^2$
	34.7 (37.2)	2.20 (1.40)	21.9	0.211
α-Methyl-	2.45 (4.9)	(1.0)		
β-Methyl-	4.81			
γ-Methyl-	7.81	1.58 (1.0)	7.46	0.184
α,α-Dimethyl-	<1			
β,β-Dimethyl-	<1			
γ,γ-Dimethyl-	2.8 (1.8)	(0.8)		

[a] Present work, in 0.025 *M* hydrochloric acid; values in parenthesis in 1 *N* nitric acid from H. Sibelius, Inaugural dissertation, Lund, 1927, quoted by W. Hückel ["Theoretical Principles of Organic Chemistry," Vol. II, Elsevier, New York, N. Y., 1958, p. 895] as equilibrium constants for cyclization ($1/K_H$).

TABLE II

HYDROLYSIS OF VALEROLACTONES[a]

Valerolactone	K_H	k_H
	16.3 (10.0)	2.16 (2.38)
β-Methyl-	0.92	1.92
δ-Methyl-	2.64 (3.72)	1.16 (2.07)
β,β-Dimethyl-	0.090	0.734
δ,δ-Dimethyl-	2.31 (3.0)	0.125 (0.155)

[a] All data at 25°, l. mole^{-1} min.$^{-1}$; present work in 0.020 *M* hydrochloric acid; values in parenthesis in 1 *N* nitric acid from H. Sibelius, Inaugural dissertation, Lund, 1927, quoted by W. Hückel ["Theoretical Principles of Organic Chemistry," Vol. II, Elsevier, New York, N. Y., 1958, p. 895] as equilibrium constants for cyclization ($1/K_H$).

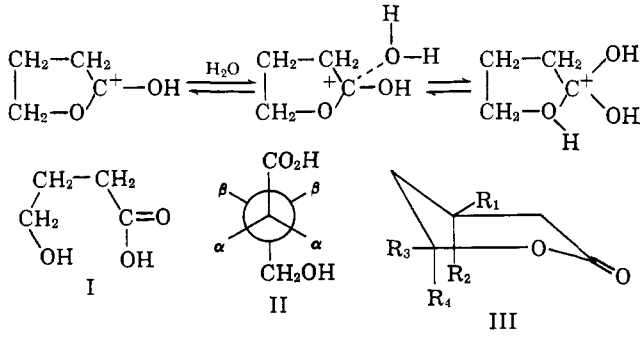
In general, substitution, particularly *gem*-disubstitution, increases the rate of ring formation.[4] However, cyclization reactions are usually irreversible, and lactonization is the only simple example of such reactions which are reversible. Here alkylation can effect both the forward and reverse reactions.

γ-Butyrolactones.—The equilibrium constants for hydrolysis (K_H) of the γ-butyrolactones (Table I; K_H = [A]/[L] for L + (H_2O) ⇌ A) decrease with methyl substitution in the order H ≫ γ-CH_3 > β-CH_3 > α-CH_3 ~ γ,γ-$(CH_3)_2$ ≫ α,α-$(CH_3)_2$ ~ β,β-$(CH_3)_2$, the last two lactones being essentially unhydrolyzed. *gem*-Dialkyl effect favoring the cyclized product has been explained[4] as being due to a combination of a favorable enthalpy effect, since the number of gauche interactions in the ring compound is less than in the open-chain derivative, and an entropy effect resulting from increased restriction to internal rotation in the acyclic compound on chain branching. For γ-hydroxy-

(1) The Puerto Rico Nuclear Center is operated for the Atomic Energy Commission by the University of Puerto Rico.
(2) O. H. Wheeler and D. S. Gamble, *J. Org. Chem.*, **26**, 3221 (1961).
(3) (a) H. Shechter, private communication; (b) C. A. Matussak, thesis, Ohio State University, 1957; (c) T. J. Dougherty, thesis, Ohio State University, 1959.
(4) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

butyric acid (I), substitution on the δ- or β-positions by interfering with either the methylene hydroxy or carboxyl group (II) will favor cyclization. In the cyclized product, the methyl groups can be accommodated in a near-planar five-membered ring without seriously increasing the nonbonded interactions.[5] In the case of γ-substitution, interference with the carboxyl group is much less since the β-methylene group is interposed. The experimental order of equilibrium constants is that expected on the basis of the effects of ring stabilization.

The acid-catalyzed hydrolysis of γ-butyrolactone proceeds by acyl–oxygen fission[6] (AAC2 mechanism), and the most probable mechanism would seem to be a rapid protonation of the carbonyl oxygen atom, followed by a slow attack of a water molecule on the protonated carbonyl carbon atom with rapid ring opening.[7] These reactions are reversible, and the slow step in the acid-catalyzed lactonization is probably the attack of the hydroxyl oxygen atom on the carbon atom of the protonated carboxylic acid group.[8]



The alkaline hydrolysis of γ-butyrolactone[2] is retarded by alkyl substitution, although the over-all rate decrease is only a factor of 4. The transition state for acid hydrolysis only differs from that for alkaline hydrolysis by possesing two additional hydrogen atoms and should have similar steric requirements.[9] Hence the methyl substituted γ-butyrolactones should undergo acid-catalyzed hydrolysis at a slightly slower rate than the parent compound, and γ-methyl-γ-butyrolactone hydrolyzed at 25° at a rate 0.72 that of γ-butyrolactone (k_H, Table I; the ratio in basic hydrolysis was 0.87[2]). Thus the large differences in the equilibrium constants must be due to enhanced rates of cyclization. It can be concluded that alkylation facilitates ring formation *by both increasing the rate of cyclization and decreasing the rate of ring opening, and that the former is the principal effect.* This results from changes in the enthalpy and entropy of activation,[4] paralleling the changes in the equilibrium thermodynamic constants, and has similar origins.

The values of the energy of activation calculated from the Arrhenius equation were found to be 15.3 and 13.9 kcal./mole for γ-butyro- and γ-methyl-γ-butyrolactone, respectively. These are somewhat smaller than previously reported data in stronger acid solution (16.8 kcal./mole for γ-butyrolactone in 1 *N* hydrochloric acid,[10a] and 16.7 kcal./mole for γ-methyl-γ-butyrolactone in 0.1 *N* hydrochloric acid[10b]).

δ-Valerolactones.—The equilibrium constants for hydrolysis of the δ-valerolactones were all decreased by substitution, in the order H >> δ-CH_3 ~ δ,δ-$(CH_3)_2$ > β-CH_3 >> β,β-$(CH_3)_2$. In the open-chain hydroxy acid, β-methyl groups will interfere with carboxylic acid group as in the corresponding γ-hydroxybutyric acid. δ-Substitution, however, will exert less interference, in accordance with the observed order.

The acid-catalyzed hydrolysis of δ-valerolactones presumably follows a similar mechanism to that of γ-butyrolactone, in which the rate-determining step is the attack of a water molecule on the protonated lactone.[7,8] Alkyl substituents near the reaction center will retard this reaction, and such retardation of ring opening has been found in substituted glutaric anhydrides.[11]

The rate constants for hydrolysis of the valerolactones (k_H see Table II) were decreased also by substitution. β-Substitution generally reduces the rates of ring opening.[4,12] However, in this case the over-all reduction in rate for all the lactones was only 1:17 and cannot entirely account for the large differences in the equilibrium constants. In particular, a small rate reduction (1:1.1) occurred for the β-methyl lactone (III, R_1 = CH_3; R_2, R_3, R_4 = H) and a further, slightly, larger reduction for the β,β-dimethyl lactone (III, R_1, R_2 = CH_3; R_3, R_4 = H). Similar results were found for 3-methyl- and 3,3-dimethylglutaric anhydride,[11b] which bear a similar stereochemical relation to the lactones. The large decreases in the values of K_H must thus be due to increases in the rate constants for lactonization (k_L) (K_H = [A]/[L] = k_H/k_L). The smaller rate constant for hydrolysis of δ,δ-dimethyl-δ-valerolactone (III, R_1, R_2 = H; R_3, R_4 = CH_3) probably arose from steric hindrance to approach of a water molecule.

The six-membered (valero-) lactones hydrolyze faster (by *ca.* 100 times; *cf.* Tables I and II) than the corresponding five-membered (butyro-) lactones.[13] This has been attributed to I-strain,[14a] since reactions involving a change in coordination number of 3 to 4 (sp^2 to sp^3 hydrid) proceed more rapidly for six-membered rings.[11a] In addition, the equilibrium constants for hydrolysis of the δ-valerolactones are much larger (again by *ca.* 100 times). However, the rate constants, for lactonization (k_L) are similar (6.35×10^{-2} and 13.3×10^{-2} l. $mole^{-1}$ $min.^{-1}$, for γ-hydroxybutyric and δ-hydroxyvaleric acid, respectively). The closure of a six-membered ring requires the bringing together of the ends of a longer chain and results in a greater loss of entropy.[14b] On the other hand, the transition state for lactonization of γ-hydroxybutyric acid (*cf.* II) is more strained than the corresponding transition state leading

(5) *Cf.* substituted cyclopentanones, O. H. Wheeler and E. E. Granell de Rodriguez, *J. Org. Chem.*, **29**, 718 (1964).

(6) F. A. Long and L. Friedman, *J. Am. Chem. Soc.*, **72**, 3692 (1950).

(7) A. S. Osborn and E. Whalley, *Trans. Faraday Soc.*, **58**, 2144 (1962).

(8) A referee has indicated that γ,γ-dimethyl-γ-valerolactone and δ,δ-dimethyl-δ-valerolactone may hydrolyze *via* oxygen–alkyl cleavage forming a tertiary carbonium ion (AAL1 mechanism).

(9) *Cf.* J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 95.

(10) (a) F. D. Coffin and F. A. Long, *J. Am. Chem. Soc.*, **74**, 5767 (1952); (b) H. S. Taylor and H. W. Close, *J. Phys. Chem.*, **29**, 1085 (1925).

(11) (a) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960); (b) O. H. Wheeler and M. A. Almeida, *J. Org. Chem.*, **27**, 2448 (1962).

(12) H. K. Hall, Jr., M. K. Brandt and R. M. Mason, *J. Am. Chem. Soc.* **80**, 6320 (1958).

(13) *Cf.* R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

(14) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); (b) the formation of cyclopentane from *n*-pentane is favored by some 8 e.u. over the formation of cyclohexane from *n*-hexane, at 25° in the gas phase [C. W. Beckett, K. S. Pitzer, and R. Spitzer, *ibid.*, **69**, 2490 (1947)].

to the six-membered lactone. The ring closure of the monophenyl ester of succinic acid is 230 times as rapid as the glutaric ester,[11a] but this has been attributed to anchimeric assistance from the carboxylate anion.

Experimental

Lactones.—δ-Valerolactone was obtained by depolymerizing its commercially available polymer by distilling with red lead.[15] β-Methyl-δ-valerolactone was a commercial sample (Aldrich Chemical Co.). β,β-Dimethyl-δ-valerolactone was prepared by reduction of β,β-dimethylglutaric anhydride with sodium in ethanol.[16] δ,δ-Dimethyl-δ-valerolactone was prepared by reaction of glutaric anhydride with 2 equiv. of methylmagnesium iodide.[17] The physical constants of the valerolactones are given in Table III. The γ-butyrolactones were those used in a previous study.[2]

TABLE III

PHYSICAL CONSTANTS OF VALEROLACTONES[a]

Valerolactone	B.p., °C. (mm.)	$n^{25}D$
δ-	65 (3 mm.) [88 (4 mm.)][b]	1.4527 [1.4568[20]][b]
β-Methyl-	77 (8 mm.) [110–111 (15 mm.)][c]	1.4482 [1.4495][c]
δ-Methyl-	95 (9 mm.) [113 (20 mm.)][b]	1.4508 [1.4589[20]][d]
β,β-Dimethyl-	110 (10 mm.) [118–120 (20 mm.)][e]	1.4480
δ,δ-Dimethyl-	96 (5 mm.) [90 (3 mm.)][b]	1.4475 [1.4497[20]][b]

[a] Lit. values in brackets. [b] Ref. 18. [c] R. I. Longley, Jr., and W. S. Emerson, *Org. Syn.*, **35**, 87 (1955). [d] Ref. 19. [e] H. N. Rydon, *J. Chem. Soc.*, 594 (1936).

δ-Methyl-δ-valerolactone.—Ethyl acetoacetate (60 g.) was added to dry ethanol (200 ml.) containing sodium (6.5 g.), and ethyl β-bromopropionate (51 g.) in ethanol (50 ml.) then was added dropwise with stirring. The solution was heated to reflux for 4 hr. and worked up to give diethyl δ-acetoxyglutarate (25 g.), b.p. 138–142° (9 mm.), $n^{25}D$ 1.4361. The ester was refluxed with concentrated hydrochloric acid (250 ml.) for 6 hr. giving 5-ketohexanoic acid (25 g.), b.p. 125–130° (9 mm.), $n^{25}D$ 1.4367. The acid (10 g.) was dissolved in 5% sodium hydroxide (100 ml.) and treated with sodium borohydride (1 g.) in water (10 ml.). The solution was left at room temperature overnight, acidified with concentrated hydrochloric acid, saturated with salt, and extracted continuously with ether to give the lactone, b.p. 95° (9 mm.), $n^{25}D$ 1.4508 (lit. b.p. 113° at 20 mm.[18], $n^{20}D$ 1.4589[19]).

Equilibrium Constants.—The lactone (*ca.* 0.5 g.) was dissolved in 0.025 *M* hydrochloric acid (50 ml.) and immersed in a constant temperature bath at 25.0 ± 0.1° for up to 5 days. Aliquots were withdrawn, diluted with ice–water (20 ml.), and titrated with 0.02 *N* sodium hydroxide, using rapid magnetic stirring to avoid saponification of the lactone. Reproducible results were readily obtained.[20] Some samples were treated with an excess of sodium hydroxide, left at room temperature overnight, and back titrated with hydrochloric acid to determine the purity of the lactone.

Rate Constants.—The kinetic runs were carried out in the same manner by titrating aliquots at intervals of 10 to 60 min. Several aliquots were also left for 3 to 5 days to measure the equilibrium point. The pseudo first-order rate constants were determined from the slope of the linear plot of ln $(\chi_e - \chi)$ against time, using the kinetic relation,[21] $k't = (\chi_e/a) \ln [\chi_e/(\chi_e - \chi)]$, where a is the initial concentration of lactone, χ_e is the equilibrium concentration of liberated acid, and χ is the concentration of liberated acid at any time t. The rate constants (k_H) are expressed (Tables I and II) as second-order rate constants independent of the concentration of acid catalyst (see Table I; $k_H = k'_H/[H^+]$[18]).

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(15) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).

(16) S. S. G. Sicar, *J. Chem. Soc.*, 898 (1928); A. Burger and A. Hafstetter, *J. Org. Chem.*, **24**, 1290 (1959).

(17) G. Koppa and W. Rohrmann, *Ann.*, **509**, 259 (1934).

(18) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).

(19) M. Hudlicky, *Chem. Listy*, **45**, 380 (1952).

(20) *Cf.* F. A. Long, W. F. McDevit, and F. B. Dunkle, *J. Phys. Chem.*, **55**, 813 (1951).

(21) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 19.

Lactam Formation through Aminolysis of α-Amino-γ-butyrolactone. 2-Amino-4-hydroxybutyramides and 1-Aryl 3-Aminopyrrolidin-2-ones

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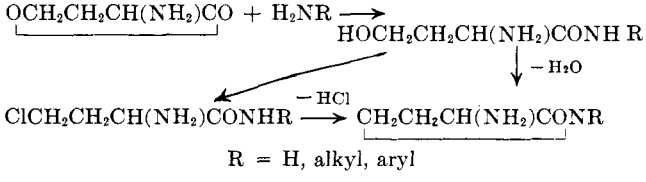
Reactions of α-amino- or α-benzamido-γ-butyrolactone with amines, leading to 1-aryl 3-amino- or 1-aryl 3-benzamidopyrrolidin-2-ones, or to α-benzamido-γ-hydroxybutyr-N-alkyl amides, are described. A mechanism is postulated for direct conversion of α-amino-γ-butyrolactone into 1-aryl 3-aminopyrrolidin-2-one, based on an unfavorable equilibrium for γ-hydroxybutyr-N-aryl amide formation and on irreversible oxygen–alkyl fission to α-amino-γ-arylaminobutyric acid, followed by direct γ-lactamization. Experiments using γ-butyrolactone and δ-valerolactone with aromatic amines demonstrate the dependence of reaction rate and of cyclization on the ring stability of starting and resulting compounds. Cyclization of γ-reactive butyr-N-alkyl amides to a lactonic, iminolactonic, or lactamic (γ-aminating) ring, determined by salt formation ability as well as by ring stability, is studied.

α-Amino-γ-butyrolactone (homoserine lactone) derivatives have been used for γ-amination by O-alkyl fission[1-3] or by γ-halogenation and appropriate subsequent amination.[1,3] In the present work, the application of homoseryl amides as possible intermediates in the γ-amination of α-amino-γ-butyrolactone was studied. Cyclization of such amides into α-amino-γ-butyrolactams in an intramolecular reaction or, indirectly, following γ-halogenation, was examined. The reactions in question might be formally postulated.



(1) M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Res. Council Israel*, **7A**, 173 (1958).

(2) G. Talbot, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **36**, 593 (1958).

(3) T. Sheradsky, Y. Knobler, and M. Frankel, *J. Org. Chem.*, **26**, 1482 (1961).