Kinetics and Mechanism of Iodolactonization of γ,δ-Unsaturated Acids[1]

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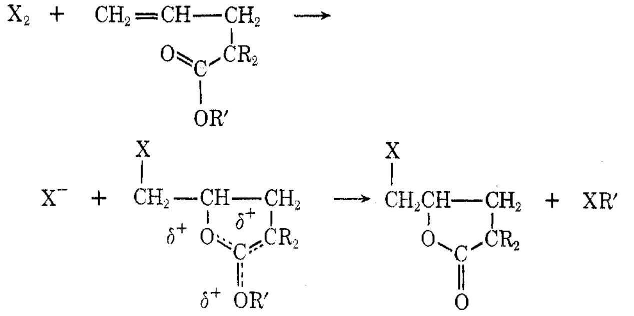
The kinetics of iodolactonization of 4-pentenoic acid (I), 2-phenyl-4-pentenoic acid (II), and 2,2-diphenyl-4-pentenoic acid (III) in chloroform have been studied at several temperatures using ^{131}I-labeled iodine. The rate law is given by the expression rate = $k_3(\text{acid})(\text{I}_2)^2$. Activation parameters which have been obtained are (acid, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta G^{\ddagger}$): I, 3.3, −59, 21; II, 5.8, −51, 21; III, 9.0, −28, 17. A mechanism is postulated and discussed.

The iodolactonization of γ,δ-unsaturated acids has been studied by Bougault,[3] Linstead,[4] and Van Tamelen.[5] Arnold, *et al.*,[6] proposed a general mechanism for the reaction of electrophilic reagents and γ,δ-unsaturated acids and esters.



Later, it was shown in a qualitative way that an increase of electron density on the carbonyl group[7] and/or the presence of substituents at the α position of the carboxylic acids[8,9] increases the rate of the iodolactonization.

Our kinetic investigations were undertaken in order to obtain quantitative rate information pertinent to the iodolactonization of γ,δ-unsaturated acids referring specifically to the effects caused by substituents on the α position of the acids.

Experimental Section

Materials.—4-Pentenoic acid was obtained from the Chemical Procurement Laboratories; 2-phenyl-4-pentenoic acid and 2,2-diphenyl-4-pentenoic acid were synthesized according to known procedures.[10,11] All the other chemicals were reagent grade and were used without further purification.

Radioactive iodine was used in the experiments. Solutions of the tagged iodine were prepared by air oxidation of aqueous solutions of Na^{131}I (specific activity 5 mCi ml^{-1}) to which a few drops of 0.1 M hydrochloric acid had been added. The iodine formed was immediately extracted into a solution of nonactive iodine in chloroform. The solution was treated with sodium sulfate and the concentration of iodine was determined by titration with thiosulfate. The solution was diluted with chloroform to the desired concentration of iodine. The final specific activity of the solution was determined (approximately 0.02 mCi ml^{-1}).

Product Analysis.—The products of the reaction of 4-pentenoic acid, 2-phenyl-4-pentenoic acid, and 2,2-diphenyl-4-pentenoic acid with iodine were prepared according to known procedures[9] with the exception that a 1:2 mole ratio of acid to iodine was used. The products were identified by means of a carbon and hydrogen analysis. The yields obtained were, respectively, valeric acid 4-hydroxy-5-iodo-γ-lactone, 77%; valeric acid 4-hydroxy-5-iodo-2-phenyl-γ-lactone, 79%; valeric acid 4-hydroxy-2,2-diphenyl-γ-lactone, 88%. Although the yields of these products were not determined in the solutions used in the kinetic experiments, the experimental conditions were close to those used in the product determinations. The products are stable in chloroform solution for several weeks.

Product Separation and Identification.—A 0.050 M solution (5 ml) of the tagged iodine in chloroform was mixed with 5 ml of a 0.025 M solution of the 4-pentenoic acid in chloroform. Meanwhile a chromatographic plate was wetted with a buffer solution of pH 7 and 2 drops of a 10% thiosulfate solution was applied at the origin. After 2 hr, a 0.1-μl aliquot of the reaction mixture was withdrawn and applied to the plate at the origin over the thiosulfate solution so that iodine was reduced to iodide and the reaction was quenched. The chromatographic plate was placed in an electrophoresis cell with the application point turned to the cathode. A force field of 12.5 V cm^{-1} was maintained for 10 min. By radiometric determination and by autoradiography it was possible to determine the composition of the radioiodide-containing products. One fraction was identified as iodolactone by treatment with hydroxylamine (transformation into hydroxamic acid) and ferric chloride, and the second fraction was identified as iodide, employing lead acetate.

Kinetic Experiments.—The kinetic runs were performed at constant temperature and in the absence of light. Individual kinetic runs were started by mixing a known volume of tagged iodine in chloroform with a known volume of the γ,δ-unsaturated acid in chloroform at the same temperature. After mixing (zero time) 0.1-μl aliquots were withdrawn at regular intervals of time and immediately applied to the chromatographic plate. Separation of the two fractions was performed as above.

The radioactivity of the two fractions (iodolactone and iodide) was determined with the aid of a geiger gas flow detector chromatograph (Nuclear Chicago, Model Actigraph III). The percentage of the radioiodolactone over the total of the radioiodine was calculated.

Isotopic Exchange.—A 0.035 M chloroform solution (5 ml) of the δ-iodo-γ-valerolactones prepared with nonactive iodine, and 5 ml of a 0.035 M chloroform solution of the tagged iodine were mixed (zero time) at several temperatures (0.0, 10.0, 20.0, and 32.0°); 0.1-μl aliquots were withdrawn at regular intervals of time; and the formation of radioiodolactone was followed as above. At 0.0, 10.0, and 20.0° there was no formation of radioiodolactone within 300 hr. At 32° the formation of 1% of the radioiodolactone was observed after 75 hr. Thus it was established that the isotopic exchange between the δ-iodo-γ-lactone and ^{131}I is a very slow reaction, and that the radioiodolactone must be formed in the direct reaction.

Results

It was shown in this work that, in chloroform solution, 1 mol of the γ,δ-unsaturated acid reacts with 2 mol of iodine, giving rise to 1 mol of iodolactone and 1 mol of hydrogen triiodide. This explains why the reac-

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[2] Abstracted from M.S. Thesis of S. C. M.

[3] J. Bougault, *Ann. Chim. Phys.*, **14**, 145 (1908); **15**, 296 (1908).

[4] R. P. Linstead and C. May, *J. Chem. Soc.*, 2565 (1927).

[5] E. E. Van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, **76**, 2315 (1954).

[6] R. T. Arnold, M. Moura Campos, and K. L. Lindsay, *J. Amer. Chem. Soc.*, **75**, 1044 (1953).

[7] M. Moura Campos, *An. Acad. Brasil. Ciênc.*, **27**, 405 (1955).

[8] M. Moura Campos, *Chem. Ber.*, **93**, 1075 (1960).

[9] M. Moura Campos and L. do Amaral, *Arch. Pharm. (Weinheim)*, **298**, 92 (1965).

[10] H. Veldstra and C. Van Westeringh, *Recl. Trav. Chim. Pays-Bas*, **70**, 1113 (1951).

[11] R. T. Arnold, W. E. Parham, and R. M. Dodson, Jr., *J. Amer. Chem. Soc.*, **71**, 2439 (1949).

tion, when performed with 1 mol of the acid and 1 mol of iodine in chloroform solution, gives a maximum yield of 50% of iodolactone.[9]

The reaction of 4-pentenoic acid, 2-phenyl-4-pentenoic acid, and 2,2-diphenyl-4-pentenoic acid with iodine in chloroform solution, was studied at several temperatures.

For each acid at the various temperatures several kinetic runs were made in which the concentration of iodine or the concentration of the acid was varied and the initial velocity of the reaction as function of the concentration was determined. The calculated per cent of iodolactone formed was plotted against time, and the tangent at zero time was determined graphically. The slopes of the tangents gave the initial velocity of the reaction expressed in per cent of the iodolactone formed per unit of time. With those values and the initial concentration of the acids the slopes could be expressed in moles of iodolactone formed per unit of time (Table I). One notices from the values of Table I that the rate of the reaction is first order in the acid concentration and second order in iodine concentration. The rate law is

$$\text{rate} = k_3(A)(I_2)^2$$

TABLE I

INITIAL RATES[a] OF THE REACTION OF 4-PENTENOIC ACID (I), 2-PHENYL-4-PENTENOIC ACID (II), 2,2-DIPHENYL-4-PENTENOIC ACID (III) AND IODINE, AND RATE CONSTANTS, IN CHLOROFORM SOLUTION AT 32°, AS A FUNCTION OF THE CONCENTRATIONS OF THE REAGENTS

C_0 I, M	C_0 iodine, M	Iodolactone, M min^{-1}	k_3, M^{-2} min^{-1}
0.140	0.0250	5.8×10^{-5}	6.6×10^{-1}
0.070	0.0250	2.5×10^{-5}	6.4×10^{-1}
0.070	0.0125	7.5×10^{-6}	6.8×10^{-1}
0.0350	0.0350	2.9×10^{-5}	6.6×10^{-1}

C_0 II, M	C_0 iodine, M	Iodolactone, M min^{-1}	k_3, M^{-2} min^{-1}
0.100	0.0250	5.5×10^{-5}	8.8×10^{-1}
0.0500	0.0250	2.7×10^{-5}	8.8×10^{-1}
0.0250	0.0250	1.3×10^{-5}	8.6×10^{-1}
0.0500	0.0125	8.0×10^{-6}	1.0×10^{0}

C_0 III, M	C_0 iodine, M	Iodolactone, M min^{-1}	k_3, M^{-2} min^{-1}
0.00750	0.00750	1.5×10^{-4}	3.7×10^{2}
0.00750	0.00375	4.0×10^{-5}	3.8×10^{2}
0.00750	0.001875	9.4×10^{-6}	3.6×10^{2}
0.001875	0.00750	3.8×10^{-5}	3.8×10^{2}

[a] In moles of δ-iodo-γ-lactone formed per minute.

From the values of the initial velocity, the initial concentration of the acids, and the initial concentration of iodine the values of k_3 were calculated (Table II).

TABLE II

RATE CONSTANTS[a] FOR THE REACTION OF 4-PENTENOIC ACID (I), 2-PHENYL-4-PENTENOIC ACID (II), AND 2,2-DIPHENYL-4-PENTENOIC ACID (III) AND IODINE, IN CHLOROFORM SOLUTION, AT SEVERAL TEMPERATURES

	0.0°	5.0°	10.0°	15.0°	20.0°	25.0°	32.0°	40.0°
I	0.35		0.41		0.51		0.66	
II	0.27		0.40		0.60		0.90	
III		69	77	98	200	340	370	480

[a] The constants are expressed in M^{-2} min^{-1}.

Arrhenius plots of log k_3 vs. $1/T$ for the reaction of 4-pentenoic acid, 2-phenyl-4-pentenoic acid, and 2,2-diphenyl-4-pentenoic acid with iodine gave reasonably straight lines from which the activation energy, E_a, was determined by least squares analysis (Table III). The enthalpy of activation, $\Delta H^{\neq}$, was obtained by subtracting RT from E_a. The entropy of activation, $\Delta S^{\neq}$, was calculated from the formula given by Schaleger and Long.[12] The activation parameters are shown in Table III.

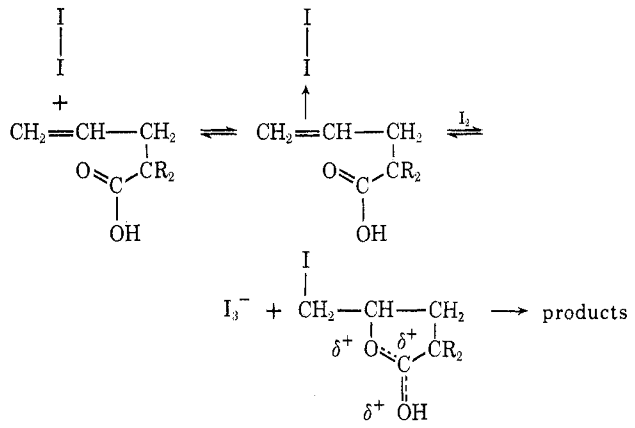
TABLE III

ACTIVATION PARAMETERS FOR THE REACTION OF 4-PENTENOIC ACID (I), 2-PHENYL-4-PENTENOIC ACID (II), AND 2,2-DIPHENYL-4-PENTENOIC ACID (III) AND IODINE IN CHLOROFORM SOLUTION

	E_a, kcal mol^{-1}	$\Delta H^{\neq}$, kcal mol^{-1}	$\Delta S^{\neq}$, eu	$\Delta G^{\neq}$, kcal mol^{-1}
I	3.9	3.3	−59	21
II	6.4	5.8	−51	21
III	9.6	9.0	−28	17

Discussion

From the data obtained in this work it is possible to propose a more detailed mechanism for the iodolactonization of γ,δ-unsaturated acids than that proposed by Arnold, *et al.*[6]



In accordance with the general mechanism of the addition reaction of halogens to alkenes in poorly ionizing solvents,[13,14] the iodolactonization of γ,δ-unsaturated acids starts by the formation of a complex between iodine and the double bond of the acids. In poorly ionizing media, as in chloroform solution, the formation of the intermediate ion, a reaction that requires charge separation, is aided by a second molecule of iodine, which helps to disperse the negative charge by formation of the triiodide ion I_3^-. The reaction is aided also by the formation of a cation whose positive charge is dispersed by resonance. The formation of the intermediate cation may occur in a preequilibrium step in which an iodine–carbonium, or iodonium ion,[15] is formed, followed by cyclization. It may also occur by a concerted reaction.

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(12) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 7 (1963).

(13) E. P. White and P. W. Robertson, *J. Chem. Soc.*, 1509 (1939).

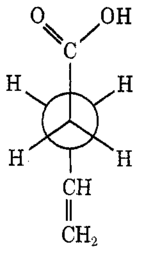
(14) K. Yates and W. V. Wright, *Can. J. Chem.*, **45**, 167 (1967).

(15) A. Hassner and C. C. Heathcock, *Tetrahedron Lett.*, **No. 19**, 1125 (1964).

The values of the entropy of activation become more negative from the reaction of iodine with 2,2-diphenyl-4-pentenoic acid to the reaction of iodine with 4-pentenoic acid, while the values of the enthalpy of activation increase from the reaction of iodine with 4-pentenoic acid to the reaction of iodine with 2,2-diphenyl-4-pentenoic acid (Table III).

The formation of the complex between iodine and the acid probably occurs as a fast step in each of the systems studied.[12] The very high negative values of the entropy of activation indicate a high degree of order in the activated complex with respect to the reactants, which is as expected for a third-order electrophilic addition process.

The increase in the measured entropy of activation from the reaction of iodine with 2,2-diphenyl-4-pentenoic acid (−28 eu) to the reaction with 4-pentenoic acid (−59 eu) is at least partly explained by a conformation analysis of the acids. For the 4-pentenoic acid the more stable conformation should be the anti (I); for the 2-phenyl-4-pentenoic acid there are two stable conformations (IIa and IIb); for the 2,2-diphenyl-4-pentenoic acid there are three stable conformations (IIIa, IIIb, and IIIc). As the conformations IIb of the 2-phenyl-4-pentenoic acid, and IIIb and IIIc for the 2,2-diphenyl-4-pentenoic acid, are appropriate to the formation of the intermediate cyclic cations, there is an increase of the population of the appropriate conformation for the reaction from the 4-pentenoic acid to the 2,2-diphenyl-4-pentenoic acid.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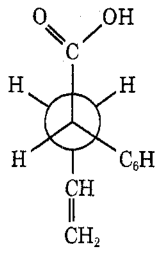
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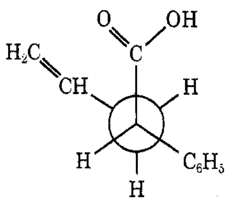
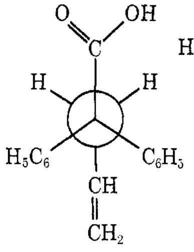
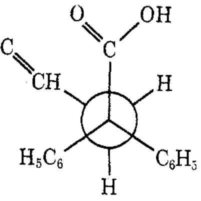

IIb


IIIa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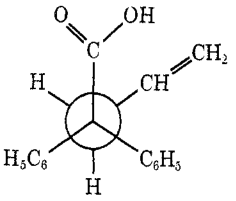
IIIc

The increasing values of the enthalpy of activation from 4-pentenoic acid to 2,2-diphenyl-4-pentenoic acid are consistent with the eclipsed conformation of the cyclic transition state, since repulsion between phenyl hydrogens and those β to the carbonyl group is expected to contribute to the energy of activation.

Registry No.—I, 591-80-0; II, 1575-70-8; III, 6966-03-6; iodine, 7553-56-2.

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Notes

Syntheses of Several 1,3-Thiazine Derivatives with Polyphosphate Ester

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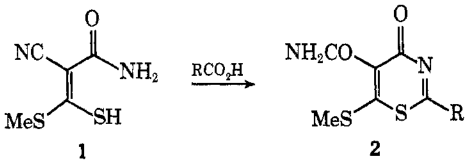
In previous work,[1] 3-alkylthio-2-cyano-3-mercaptoacrylamide (**1a**) and 3-alkylthio-2-cyano-3-mercaptothioacrylamide (**1b**) promised to be useful intermediates for synthesizing 4-keto-1,3-thiazine derivatives and 4-thioketo-1,3-thiazine derivatives, respectively.

It has been shown recently by Kanaoka and coworkers[2] that benzothiazoles can be obtained by condensation of *o*-mercaptoanilines and free carboxylic acids in the presence of polyphosphate ester (PPE). This suggested that a similar condensation of the mercaptoamides with acids and PPE might provide a good route to 1,3-thiazine derivatives.

Pursuing this possibility, we have found that reaction of the cyanoamide **1** with an aromatic acid and PPE in refluxing chloroform gives the 5-carbamoyl-6-methylthio-1,3-thiazin-4-ones (**2**) in 27–90% yield. The cyano thiazines could not be detected.



1 **2**

The structure **2** is consistent with analyses and spectral data. Mass spectral data for **2** show a P − 47 ion characteristic for the SCH_3 group.[3] The nmr spectrum (DMSO-d_6) of **2a** gives a singlet methyl signal at δ 2.65, a multiplet phenyl signal at 7.70, and a broad amino signal at 8.20, which disappears on deuterium exchange. Ir spectral data of **2a** show a very strong peak of the

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(1) (a) M. Yokoyama, *Bull. Chem. Soc. Jap.*, **44**, 1610 (1971); (b) M. Yokoyama, *J. Org. Chem.*, **36**, 2009 (1971).

(2) Y. Kanaoka, T. Hamada, and O. Yonemitsu, *Chem. Pharm. Bull.*, **18**, 587 (1970).

(3) Mass spectral data for 6-methylthio-2,3-dihydro-1,3-thiazin-4-one (thione) derivatives showed a P − 47 ion which was considered to be a fragment of the P − SCH_3 ion (see ref 1).