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MECHANISTIC STUDIES ON THE DOUBLE ACTIVATION METHOD FOR THE SYNTHESIS OF MACROCYCLIC LACTONES

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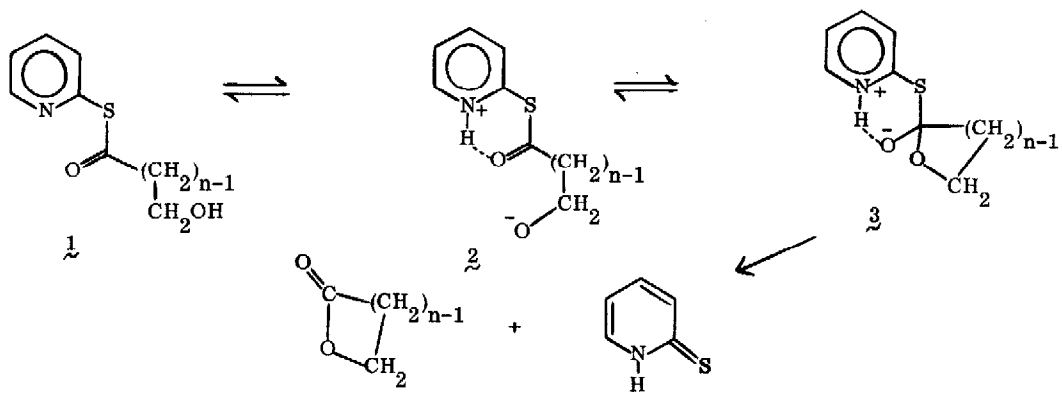
The idea of generating macrocyclic lactone systems by an internal esterification in which hydroxyl and carboxyl functions are simultaneously activated by internal proton transfer from hydroxyl to carbonyl led to the discovery of a very effective cyclization of hydroxy acids via 2-pyridinethiol esters (1).[1] The sort of mechanism envisaged for this "double activation" method for lactonization may be represented as shown in Scheme I. Formation of the doubly-activated intermediate 2 leads to a collapse to the tetrahedral carbonyl adduct 3 from which lactone is formed by the usual elimination path.



Scheme I

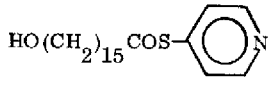
Most of the early work[2-4] on the new lactonization method was devoted to the determination of synthetic utility and scope. For example, the formation of the macrocyclic structures characteristic of brefeldin, carpaine, vertaline, erythronolide B and vermiculine could be demonstrated. This note reports a study of the kinetics and mechanism of the cyclization process, a matter of interest to us not only because a mechanistic concept was central to the discovery of the method, but also for the purpose of laying a sound foundation for further development.

The 2-pyridinethiol ester (4) (1, n=15) of 16-hydroxy-n-hexadecanoic acid (prepared from the hydroxy acid, triphenylphosphine and 2,2'-dipyridyl disulfide in benzene)[1,5] was selected as the main substrate for kinetic studies since it undergoes conversion upon heating in benzene solution (10^{-5} M initial concentration)

at 80.0° to hexadecanolide in good yield.[6] The rate of cyclization of 4 under these conditions was found to follow first order kinetics:[7]

$$d\frac{[\text{lactone}]}{dt} = k_1[\text{thioester}].$$

The rate of lactonization was not increased by the addition of several equivalents of any of the following substances: triphenylphosphine, triphenylphosphine oxide, triethylamine, triamylamine, 2-pyridinethione or acetic acid. This result indicates the absence of acid or base catalysis and also the lack of catalysis by various co-products or possible contaminants. In contrast to the smooth lactonization of the 2-pyridinethiol ester (4), the isomeric 4-pyridinethiol ester (5) of 16-hydroxy-n-hexadecanoic acid afforded no lactone under the same conditions used for 4 or even under more forcing circumstances. Obviously, proton chelated structures such as depicted in Scheme I are not possible with 5. Similarly, no cyclization could be detected using the phenylthiol ester of 16-hydroxy-n-hexadecanoic acid with or without added tertiary amine.



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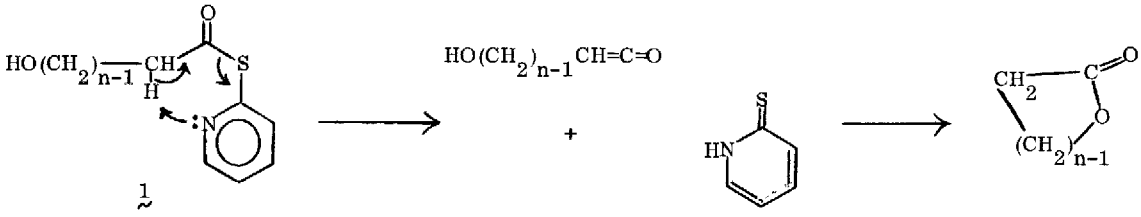
One mechanism for the lactonization of 2-pyridinethiol esters (1) which is quite different from that shown in Scheme I, but which is consistent with the observations described above, is outlined in Scheme II.



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Scheme II

The ω-hydroxy ketene intermediate in this Scheme could be formed by the cycloelimination shown and could give rise to lactone by the well known pathway for reaction of ketenes with alcohols. Three different lines of evidence have been obtained which seem sufficient to allow exclusion of Scheme II from further consideration.

(1) Lactonization of O-deuterated 4 (under the usual anhydrous conditions in benzene) afforded lactone which was completely devoid of deuterium by mass spectral and pmr analysis (presence of deuterium at C-2 would be expected).

(2) The rate of lactonization of O-deuterated 4 (80° in benzene) was 1.36 ± 0.09 slower than that for non-deuterated 4 (no kinetic isotope effect is predicted for rate-limiting ketene formation).

(3) Lactonization still occurs with the 2-pyridinethiol esters of α, α-dimethylated ω-hydroxy acids (no α-H available for ketene formation).

The mechanistic studies reported herein are completely consistent with the reaction pathway indicated in Scheme I or a closely related variant in which the transfer of a proton to the carbonyl oxygen and the attachment of oxygen to the carbonyl carbon are to some extent synchronized. Both processes can be considered

as essentially "double activation" pathways. A clear experimental distinction between the two looms as an unusually formidable problem.

The relative rates of lactonization for a series of ω-hydroxy-n-alkanoic acid 2-pyridinethiol esters were measured in benzene solution at 80° with the results summarized in the following table.[7,8]

RELATIVE RATES OF FORMATION OF $(CH_2)_n$—C=O FROM 2-PYRIDINETHIOL ESTERS

Ring size (n + 2)	Relative Rate (80°C, C_6H_6)	
12	0.2	
13	0.36	
14	1.0	(standard)
15	1.0	
16	2.5	
17	1.9	
18	1.35	
19	0.55	
20	1.55	
21	0.6	

The rates of formation of twelve- to twenty-one-membered lactones were all much lower than the rates of formation of δ-valerolactone or ε-caprolactone, but not very much different from one another (largest spread, factor of ca. 12 between twelve- and sixteen-membered cases). These data indicate that the double activation method should be applicable at least up to a ring size of twenty-one. An interesting (but not very large) rate alternation appears to be occurring in the eighteen- to twenty-one-membered range. In general, factors other than ring size can be expected to affect cyclization rates; these include (1) presence of substituents on or heteroatoms in the chain being cyclized, or (2) presence of double, triple or endocyclic bonds which restrict rotation along the chain. These factors may well dominate the effect of ring size itself in determining rates or efficiency of cyclization.[9]

References and Notes

1. E. J. Corey and K. C. Nicolaou, J. Am. Chem. Soc., 96, 5614 (1974).
2. E. J. Corey, K. C. Nicolaou and L. S. Melvin, Jr., ibid., 97, 653, 655 (1975).
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4. E. J. Corey, P. Ulrich and J. M. Fitzpatrick, ibid., 98, 222 (1976).
5. T. Mukaiyama, R. Matsueda and M. Suzuki, Tetrahedron Letters, 1901 (1970).
6. All kinetic and preparative experiments were conducted under rigorously anhydrous conditions in an argon atmosphere.
7. Rates were determined by quantitative vapor phase chromatographic (vpc) analysis for lactone (SE-30 column, electronic signal integration using internal standard).
8. Relative rates were determined by vpc analysis of mixtures of pairs of ω-hydroxy 2-pyridinethiol esters to measure the relative amounts of lactone produced. Pairs of esters differing by both one and two carbon atoms were measured to obtain an internal double check of the data; relative rates for homologous esters are good to ca. 0.1.
9. This research was assisted financially by a grant from the National Institutes of Health.