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FORMATION OF β-LACTONES IN THE IODOLACTONIZATION REACTION

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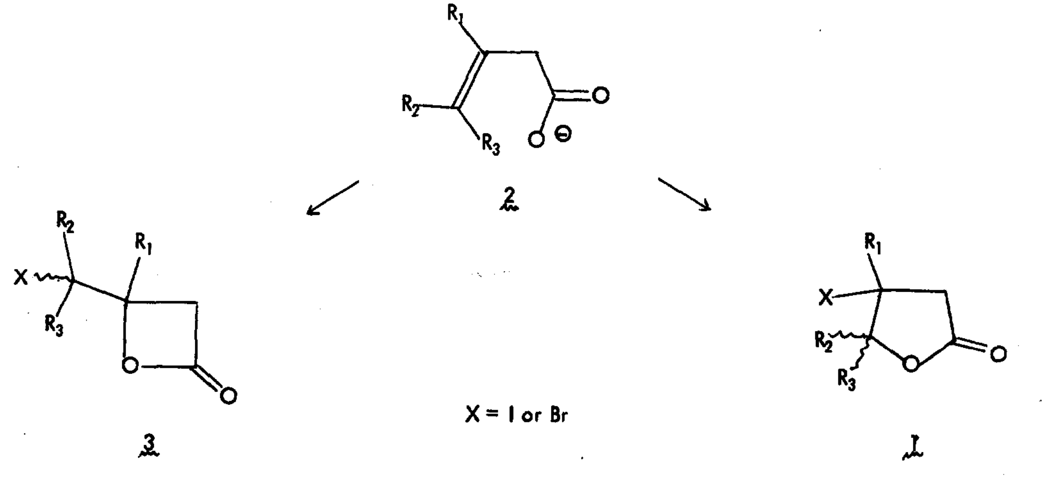
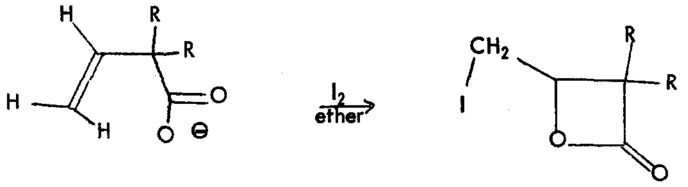
Interactions of electrophiles with multiple bonds produce positively charged intermediates leading to addition reactions.[1] In certain cases the charged intermediates can be trapped by a nucleophilic center located within the same molecule resulting in the formation of a new ring. Among the best known examples of such transformations are halolactonization reactions in which unsaturated carboxylic acid salts when treated with halogens are changed into halogenated lactones.[2,3,4].

It has been an established rule that β-iodo-γ-lactones, 1 (X= I), are formed when β, γ -unsaturated carboxylate salts, 2, are treated with iodine in the iodolactonization reaction.[5] However, recent publications on the related bromolactonization reaction have shown that β-lactones, 3 (X= Br) are the principal products from certain β,γ-unsaturated acids.[2,3] From the published information, the size of the lactone ring appears to depend on the kind of halogen used. In this paper we show that the difference in ring size results from differences in experimental procedures for the two reactions, not from differing reactivity of the halogens. We find that when the iodolactonization is conducted under conditions similar to bromolactonization, the products formed from certain β, γ-unsaturated acids are in fact γ-iodo-β-lactones, 2 ⟶ 3 (X= I). This finding broadens the scope of a new method for synthesizing β-lactones.[3]



The usual procedure for iodolactonization calls for a substantial quantity of potassium iodide in addition to iodine. With long reaction times and added potassium iodide, β, γ-unsaturated acids produce γ-lactone products.[4,5]. However, when short reaction times are employed in the absence of potassium iodide, certain β, γ-unsaturated acids form γ-iodo-β-lactones. Thus 2,2-dimethyl-3-butenoic acid[6] (1.14 g, 0.01 mol) was dissolved in a saturated sodium bicarbonate solution (40 ml) to produce a homogeneous solution of the carboxylate salt **4**. The solution was added dropwise over 10 min., at 0-5°, with stirring, to a solution of iodine (2.54 g, 0.01 mol) in ether (100 ml). The mixture was stirred one hour, washed with $Na_2S_2O_3$ (2X 30 ml/10 %), and washed with water (2X20 ml). The organic layer was dried (Na_2SO_4) and filtered. Evaporation of the solvent gave 1.35 g of lactone **5**:[7] mp 52-53° (recrystallized from ether/pentane); IR (nujol) 1827 cm^{-1} (β-lactone >C =O); NMR ($CDCl_3$) δ=4.46, d-d, lH, $H-\overset{|}{\underset{|}{C}}-O$; 3.00 - 3.52, m, 2H, -$CH_2I$; 1.44, s,3H, -$CH_3$; and 1.32, s, 3H, -$CH_3$. Under similar reaction conditions, 3-butenoic acid[8] afforded the iodo-β-lactone **7** as an unstable oil:[7] IR (neat) 1833 cm^{-1} (β lactone >C=O); NMR ($CDCl_3$) δ = 2.90-3.69, overlapping multiplets, 4H, -CH_2I and -CH_2-CO_2-; 4.25-4.65, lH, m $H-\overset{|}{\underset{|}{C}}-O$. In these reactions the yield of **5** is usually in the range of 70-80 % whereas the corresponding yield of **7** is much lower, 20-30%. This is in part explicable by the increased rate of ring closure expected for **4**[9].

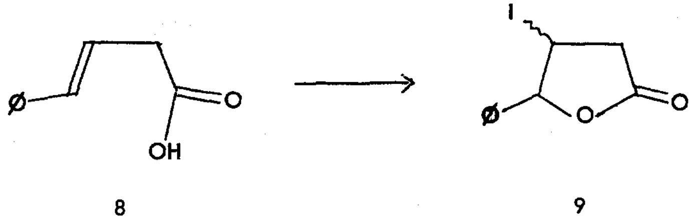


4 (R = CH_3)
6 (R = H)

5 (R = CH_3)
7 (R = H)

In order to establish that β-lactone formation was procedure-specific and not merely substrate-specific, both **4** and **6** were iodolactonized under the usual conditions[5] employing added excess KI. Although it has been generalized that the KI method of iodolactonizing β, γ-unsaturated acids produces γ-lactones, the simplest β,γ-unsaturated carboxylate, **6**, is not supposed to form an iodolactone under these conditions.[5] We have confirmed the unreactive nature of **6**[10] and have shown that with the KI method **4** is transformed into a γ-lactone, mp 55-56°, IR (neat) 1780, 1792 (sh) cm^{-1}. It is therefore apparent that the different methods of iodolactonization are responsible for the differences in ring formation. With this discovery it was tempting to generalize that the new two-phase iodolactonization procedure affords principally β-lactones from β, γ-unsaturated acids whereas the KI method affords γ-lactones. Further work is needed to qualify this generalization; we have already discovered one exception.

Styrylacetic acid, **8**, [11] is transformed into the γ-lactone **9**, regardless of which procedure is used for iodolactonization. The influence of the γ-phenyl substituent is sufficiently strong to promote γ-lactone formation even in the two-phase method.



8 **9**

The currently accepted mechanism for iodolactonization assumes the formation of a cyclic three-membered iodonium ion by electrophilic attack of a positive iodine specie upon the double bond. This three-membered cyclic iodonium ion is opened by nucleophilic intramolecular attack of the carboxylate ion to form the lactone ring.[4,5]. Although there is no concrete evidence for the three-membered iodonium ring, its intermediacy is made plausible by observed stereochemical aspects[4] of the reaction (trans addition reported for some γ-lactone products) and by recent studies demonstrating the existence of related cyclic three-membered-ring, bromonium ions.[12] At this time, it is not known whether the γ-iodo-β-lactones are formed by way of such a cyclic iodonium ion or whether the addition is stepwise in a Markownikoff sense. The regiospecificity observed in the formation of **5**, **7** and **9** cannot discriminate between these possibilities.[13]

Further work is in progress to test the scope of β-lactone formation with the new iodolactonization procedure. In particular, the stereochemistry of β-lactonization is currently being examined.

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References and Footnotes

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4. H. O. House, "Modern Synthetic Reactions", Benjamin, New York, 1965, p. 143.
5. E. E. van Tamelen and M. Shamma, J. Amer. Chem. Soc. 76, 2315 (1954).
6. A. Courtot, Bull. Soc. Chim. Fr. 35, 111 (1906).
7. All new compounds gave satisfactory analytical data except for **7**; the difficulty in this case is presumably related to its instability.
8. E. Rietz, Organic Syntheses, Coll. Vol. III, 851 (1955).
9. A. Weissberger, Ed., "The Chemistry of Heterocyclic Compounds", Interscience, New York, 1964, Vol. XIX, part 2., p. 789. A summary of steric effects on the kinetics of cyclization of β-halo-carboxylate salts.
10. Reaction time, 24 hours.
11. Styrylacetic acid was obtained from the Aldrich Chemical Co.; it was used without additional purification.
12. For a recent discussion of halonium ion intermediates see: G. A. Olah, C. L. Jeuell, and A. M. White, J. Amer. Chem. Soc. 91, 3961 (1969); and references 2 and 3 therein.
13. It is possible that the γ-iodo-β-lactones are kinetically controlled products of iodolactonization while the β-iodo-γ-lactones are thermodynamically controlled products. Some obvious experiments are being performed to test this possibility.