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A NEW GENERAL β-LACTONE SYNTHESIS

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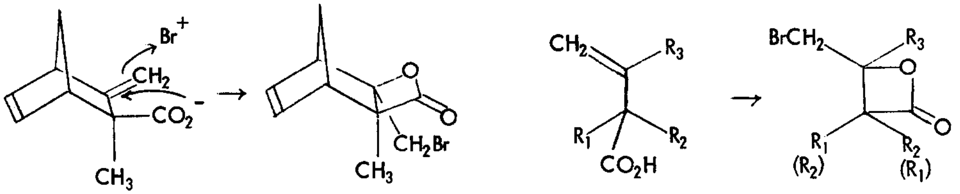
Standard general methods for synthesizing β-lactones have been discussed by Zaugg[1] and by Weissberger[2]. Since these reviews two new general methods of significant novelty have been published[3,4].

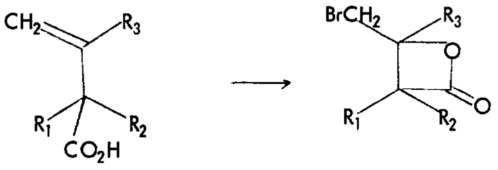
We recently reported the first instance[5] of β-lactone formation, I⟶II, during halolactonization of a β,γ- unsaturated acid. The substrate in this reaction was a carboxylate salt having the rigid norbornene skeleton. It was of interest to determine whether β-lactone formation was a property associated only with such rigid systems or whether conformationally more flexible β,γ-unsaturated acids would form β-lactones under similar conditions. We now find that conformationally less rigid, open chain β,γ-unsaturated carboxylate salts of III cyclize readily to γ-bromo-β-lactones, IV, when aqueous solutions of the salts are treated with CCl_4 or CH_2Cl_2 solutions containing one equivalent of bromine. Thus, the bromolactonization of β,γ-unsaturated acids is apparently a new general method for synthesizing β-lactones.



I II III IV

The first two cases of conformationally mobile β,γ-unsaturated acids examined were IIIa[6] (III, $R_1=R_2=CH_3$, $R_3=H$) and IIIb[7] (III, $R_1=CO_2Et$, $R_2=R_3=CH_3$). In each of these substrates the α position is blocked so that the double bond cannot become conjugated with the acid function. Bromination of sodium 2,2-dimethyl-3-butenoate[6] produced the corresponding β-lactone, IVa (83%)[8]; mp 36-37°; IR, 1840 cm^{-1}; NMR, δ=4.42, q, 1H, H-$\overset{|}{\underset{|}{\mathrm{C}}}$-O; 3.59, m, 2H, $-CH_2Br$; 1.44, s, 3H, $-CH_3$; 1.33, s, 3H, $-CH_3$. The sodium salt of IIIb[7] reacted with bromine to produce a mixture of β-lactones, IVb_1 and IVb_2 (88%). Although we have not yet been able to separate these isomers, the structures are evident from spectral analysis of the mixture. In the IR a strong β-lactone carbonyl band is present at 1837 cm^{-1} while the allylic methyl group which appears at 1.86 δ in the NMR of the starting acid has been replaced by multiplets in the region 3.58-3.95 δ corresponding to the two $-CH_2Br$ groups of the isomeric β-lactones. In addition to the singlet at 1.68 δ (3H, CH_3-$\overset{|}{\underset{|}{\mathrm{C}}}$-$CO_2Et$), two new singlets appear at 1.56 and 1.63 δ (ratio 1:2, 3H total, isomeric CH_3-$\overset{|}{\underset{|}{\mathrm{C}}}$-O).

Whether the new β-lactone forming reaction is limited to cases where the α-position is blocked was tested by using vinylacetic acid. The base catalyzed isomerization of vinylacetic acid to crotonic acid is rather facile[9]. Nevertheless, β-lactone formation is sufficiently rapid so that freshly purified[9] vinylacetic acid when dissolved in bicarbonate solution and treated with bromine affords β-lactone IVc (50%) ; bp 150-160°/1 mm[8]; IR, 1827 cm^{-1}; NMR, δ=3.29-3.82, m, 4H, $-CH_2Br$ and $-CH_2-CO_2-$; 4.53 to 4.77, m, 1H, -$\overset{|}{\underset{|}{\mathrm{C}}}$H-O-. The positions of these peaks compare favorably with chemical shifts of similar protons in IVa and propiolactone[10].



III

IV

IVa $R_1 = R_2 = CH_3$, $R_3 = H$

IVb_1 $R_1 = CO_2Et$, $R_2 = R_3 = CH_3$

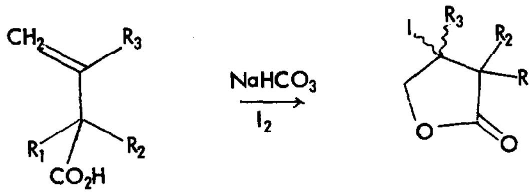
IVb_2 $R_1 = R_3 = CH_3$, $R_2 = CO_2Et$

IVc $R_1 = R_2 = R_3 = H$

Methods for the synthesis of β-lactones can be classified according to the kinds of bonds created. For example, open chain acids can be cyclized by methods in which the alkyl-oxygen bond is created. Such standard methods as the cyclization of β-halocarboxylate salts[1,2] and the diazotization of primary β-amino acids[2] fall into this category. It can be generalized that these reactions occur when an electrophilic β-carbon atom becomes attacked internally by a nucleophilic carboxylate or carboxyl group. It is likely that the new β-lactone forming reaction we are reporting is in this category.

Positive halogen atoms interact with double bonds leading to electrophilic intermediates capable of accepting nucleophiles[11]. In the Prevost reaction[12] a positive iodide ion interacts with a double bond giving an intermediate which is then intercepted by carboxylate ion to provide an iodo-ester addition product. A similar intramolecular version of this reaction leads to an iodolactone and is known as iodolactonization[13]. The corresponding process involving bromine is known as bromolactonization . Few previous systematic studies of the bromolactonization reaction have been made[13]. Perhaps no differences with the more commonly used iodolactonization reaction were expected.

The behavior of β, γ -unsaturated acids in the bromolactonization reaction, III ⟶ IV, is in direct contrast with the well-established rule that iodolactonization of β, γ-unsaturated acids leads to the formation of β-iodo-γ -lactones,[14] III ⟶ V. Based on the generally accepted principle that β-lactones are inherently less stable than γ-lactones because of ring strain, the production of the less stable isomer during bromolactonization is undoubtedly kinetically controlled. Whether the γ-lactones, V, formed during iodolactonization are thermodynamic or kinetic products remains to be demonstrated.[15] It is possible that they are in fact kinetic products also, in which case the difference in electrophilic character of the halogens may be a decisive factor in determining the size of the lactone ring formed.



III V

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References and Footnotes

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