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A NEW METHOD FOR THE SYNTHESIS OF Δ^1-BUTENOLIDES

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The Δ^1-butenolide function occurs widely in nature as part of a fused ring system such as that of eremophilenolide (1) or as a separate ring in many of the physiologically important cardiac-glycosides (2). Although a large number of synthetic approaches have been reported (3) for Δ^1-butenolide formation, they all suffer from one or more faults, the prime one being low yields. We would like to report a new method for the preparation of model Δ^1-butenolides similar to the naturally occurring ones in significantly higher over-all yields than those previously reported.

The first step in all cases was a Reformatsky reaction involving normal α-bromoesters but unusual carbonyl substrates, α-chloroketones. The use of α-chloroketones has been reported (4), but the yields were low. We have consistently been able to get good yields by careful attention to experimental details. Although the Reformatsky products were not stable long enough to get acceptable elemental analysis, the spectral data (i.r. and n.m.r.) and the subsequent conversion of these materials in high yield to known compounds left little doubt as to their structure.

Commercially available but carefully purified I and II were reacted in a dried 2:1 mixture of ether and benzene with acid washed and vacuum dried, reagent grade zinc to give chlorohydrin ester III in yields as indicated in Table I. The reaction of α-chlorocyclohexanone with methyl α-bromoacetate

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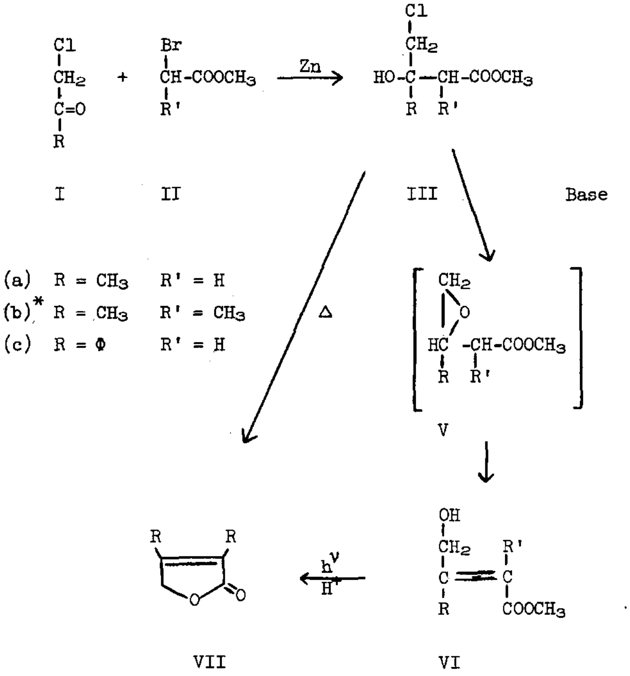
* From the Ph.D. thesis of Arch C. Sonntag

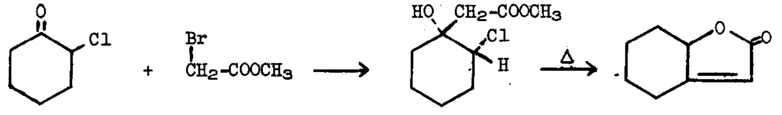
occurred in a stereospecific manner to give IV whose stereochemical assignment will be considered below. This result is consistent with the mechanism of the Reformatsky reaction as proposed by Zimmerman (5) assuming that the chlorine of chlorocyclohexanone is in an axial position at the time of reaction.

The Reformatsky products could be converted into the corresponding Δ^1-butenolide by at least one of two pathways. In one sequence IIIa was treated with slightly more than one molar equivalent of potassium hydroxide in methanol at 0° to give VIa [96% yield based on recovered starting material, b.p. 70-80°/0.5 mm; lit. (6) b.p. 90-100°/6 mm; consistent i.r. and n.m.r. spectra].



(a) R = CH_3 R' = H
(b)* R = CH_3 R' = CH_3
(c) R = Φ R' = H

* Ethyl bromoacetate was used in place of methyl bromoacetate in this experiment.



IV VIII

TABLE I

Reformatsky Reaction Yields

Compound	Yield	Boiling Point
IIIa	79%	38°/0.1 mm
IIIb	63%	68-74°/0.1 mm
IIIc	67%	130°/1 mm
IV	79%	84°/0.2 mm

The trans arrangement of the hydroxymethyl and carboxymethyl groups as well as the rest of the structure of VIa was confirmed by oxidation and hydrolysis of VIa to the known compound, mesaconic acid. The high yield and stereospecificity of the base reaction suggested epoxide Va as an intermediate. The epoxides Vb and Vc could be isolated by proper choice of base and reaction conditions [Vb, 25% yield using sodium amide in liquid ammonia, b.p. 65-75°/15 mm; C, 60.74; H, 8.92. Vc, 83% yield using potassium carbonate in acetone, b.p. 84-87°/0.1 mm; C, 68.93; H, 6.50. Vb and Vc gave a positive periodate test as well as consistent i.r. and n.m.r. spectra]. Although base treatment converted Vb to the expected products, VIb and VIIb, the reaction was not normally accomplished in this manner.

Irradiation of an acidified methanol solution of hydroxy ester VIa in a quartz cell using a 550 watt high pressure mercury arc gave the known butenolide VIIa in 74% yield [b.p. 68-78°/0.25 mm; lit. (7) b.p. 106-107°/12 mm; C, 61.47; H, 6.31; positive Ag mirror test; i.r. 1750 cm^{-1} carbonyl but no 1880 cm^{-1} band for the Δ^2-butenolide, 1640 cm^{-1} double bond; n.m.r.

3 H singlet at 2.12 ppm, 2 H singlet at 4.75 ppm and 1 H singlet at 5.71 ppm].* The reaction of IIIb under the above base conditions gave rise to a 65:35 mixture of VIb and VIIb (g.l.c. on 4 ft. Carbowax 20M column) which was not normally separated but rather was acidified and irradiated to give known butenolide VIIb in 62.5% yield based on IIIb [b.p. 86°/2 mm, m.p. 32-35°; lit. (8, 9) b.p. 64°/0.2 mm, m.p. 36-38°; C, 64.29; H, 6.37; i.r. 1750 cm^{-1} lactone but no 1880 cm^{-1} band for the Δ^2-butenolide, 1690 cm^{-1} double bond; n.m.r. 3 H singlets at 1.68 and 2.01 ppm and 2 H singlet at 4.62 ppm]. The use of the base, irradiation sequence on IIIc gave poor yields of VIIc, but the second pathway to be considered below did give excellent yields. The base reaction on IV gave only hydrolysis of the ester and some dehydrohalogenation which suggested that the hydroxyl and chlorine in IV must be _cis_ to one another and thus a different approach to lactonization was required.

The second method of converting the Reformatsky product to the appropriate Δ^1-butenolide involved a pyrolytic reaction analogous to the work of Weinstock (10) who found that methyl (_trans_-2-bromocyclopentyl) acetate was converted to a γ-lactone and ethyl bromide while the _cis_ isomer gave only HBr and olefin. Cyclization and dehydration of the chlorohydrin IV was realized by heating at 210° until gas evolution (CH_3Cl) almost ceased and then raising the temperature to 235° to dehydrate the lactone. Distillation of the residue gave VIII in 84% yield based upon recovered IV [b.p. 123°/4.7 mm, m.p. 27-28.5°; lit. (11) b.p. 108°/1 mm, m.p. 24°; i.r. 1748 cm^{-1} lactone but no 1880 cm^{-1} band for the Δ^2-butenolide, 1645 cm^{-1} double bond; n.m.r. 8 H multiplet at 2.0 ppm, 1 H broadened triplet at 4.75 ppm, and a 1 H singlet at 5.65 ppm]. The same technique was applied to IIIc to yield crystalline butenolide VIIc in 86% yield [m.p. 92-93°; lit. (12) m.p. 94°].

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* For the n.m.r. spectra, a Varian A-60 spectrometer was used.

Pyrolysis of IIIa and IIIb gave small amounts of butenolides VIIa and VIIb. The low yields can probably be attributed to the instability of IIIa and IIIb as well as the fact that the boiling points of IIIa and IIIb were close to the pyrolysis temperatures.

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