Reaction of Ketene with Aldehydes in the Presence of Zinc Carboxylic Acid Salts

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The first step of an industrial route to 2,4-hexadienoic acid (sorbic acid) is the production of a polymeric material by reaction of ketene with crotonaldehyde in an inert solvent containing a catalytic amount of a zinc salt of a carboxylic acid.[1] As part of our continuing study of ketene chemistry, we have investigated the identity of this polymeric reaction product and have inquired into the mode of its formation.

Analysis of the ir spectrum and, particularly, the nmr spectrum of the ketene–crotonaldehyde reaction product led to its tentative identification as poly(3-hydroxy-4-hexenoic acid) (1). In order to obtain verification of this structure, the polymer was reduced with lithium aluminum hydride to give 4-hexene-1,3-diol which was identical with an actual sample of the diol prepared by an independent route. This route involved the lithium aluminum hydride reduction of ethyl 3-hydroxy-4-hexenoate prepared by a Reformatsky reaction utilizing crotonaldehyde, ethyl bromoacetate, and zinc (Scheme I).

<div align="center">SCHEME I</div>
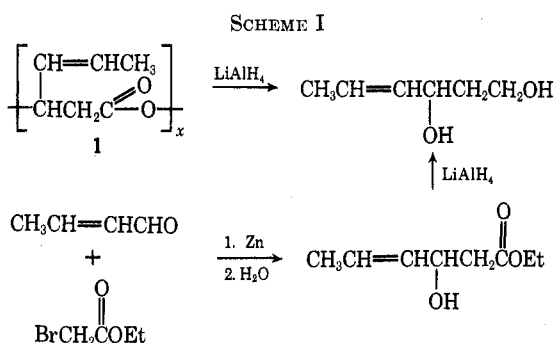
There are two general ways that polyester 1 might have been formed from ketene and crotonaldehyde. The polyester could have arisen by polymerization of 3-hydroxy-4-hexenoic acid β-lactone (2) formed initially (path a) or by the direct copolymerization of ketene and crotonaldehyde without the intermediacy of 2 (path b) (Scheme II).

Although no mechanistic work on this reaction has been published, several related pieces of work have appeared. It is generally known that ketene will react with aldehydes in the presence of a variety of catalysts to give β-lactones. In several cases, zinc salts of carboxylic acids have been shown to be effective. Hagemeyer has reported that ketene will react with aromatic aldehydes in the presence of zinc salts of fatty acids to give β-lactones.[2] Caldwell was able to isolate good yields of β-lactones by using zinc trifluoroacetate as catalyst for the reaction of ketene with aliphatic aldehydes.[3]

(1) R. N. Lacey, *Advan. Org. Chem.*, 2, 213 (1960).
(2) H. J. Hagemeyer, U. S. Patent 2,466,420 (1949).

<div align="center">SCHEME II</div>
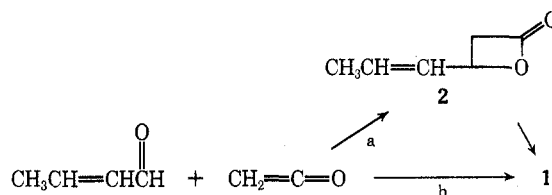
On the other hand, in some instances ketenes and aldehydes will copolymerize to polyesters directly without the intermediacy of β-lactones. Natta and coworkers have shown that dimethylketene and benzaldehyde will polymerize to poly(3-hydroxy-3-phenyl-2,2-dimethylpropionic acid) in the presence of metal alkyls or alkoxides.[4] They have shown that, at least in their particular case, the corresponding β-lactone is stable under the reaction conditions and, therefore, is not a reaction intermediate.

In order to determine whether 2 was an intermediate in the reaction of ketene with crotonaldehyde catalyzed by zinc salts of carboxylic acids, we decided to synthesize 2 and submit it to the reaction conditions. If the β-lactone were stable under these conditions, it could not have been an intermediate in the polymerization reaction.

The only synthesis of 2 is that of Hagemeyer, who presented evidence that the lactone was produced by the reaction of ketene with crotonaldehyde in the presence of boron trifluoride at −25°.[5] Hagemeyer was not able to isolate 2 but inferred its presence because of the evolution of piperylene on pyrolysis of the reaction mixture. We made several attempts to synthesize 2 by this method but none was successful. The nmr spectrum of the cold reaction mixture failed to reveal any bands characteristic of β-lactones.

Since we were unable to prepare 2, we decided to prepare the similar, yet known,[6] 3-hydroxy-4-pentenoic acid β-lactone (3). This lactone was prepared from ketene and acrolein in 70% yield by a procedure similar to that which failed for 2. As opposed to 2, lactone 3 was stable and could be distilled under vacuum at 48°.

In the presence of zinc acetate, ketene and acrolein again underwent a facile reaction, but in this case the product was poly(3-hydroxy-4-pentenoic acid) (4) (eq 1). The nmr spectrum of the crude product con-

(1)
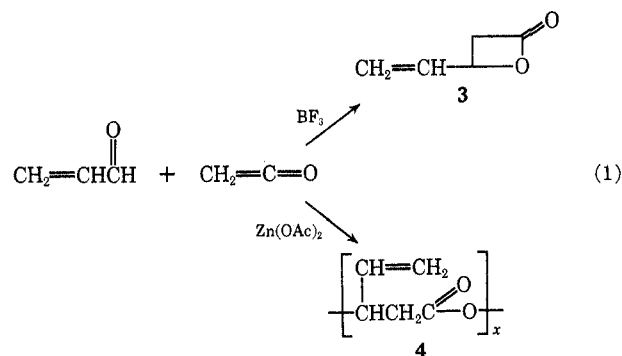
(3) R. J. Caldwell, U. S. Patent 2,739,158 (1956).
(4) G. Natta, G. Mazzanti, G. F. Pregaglia, and G. Pozzi, *J. Polym. Sci.*, 58, 1201 (1962).
(5) H. J. Hagemeyer, U. S. Patent 2,478,388 (1949).
(6) E. W. White in "Acrolein," C. W. Smith, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p 142.

tained no bands characteristic of lactone **3**. In order to determine if lactone **3** could have been an intermediate in the formation of **4**, the zinc acetate catalyzed reaction was carried out with **3** initially present. During reaction the lactone was not consumed and was recovered by distillation from the reaction mixture. In this reaction, then, the polyester was not formed by polymerization of an intermediate β-lactone, but must have arisen by a process not involving the lactone.

Although the mechanism for the direct conversion of ketene and aldehydes to polyesters in the presence of zinc carboxylic acid salts is unknown at present, it is interesting to note that zinc acetate is probably not acting as a Lewis acid. In the reaction of ketene with acrolein (eq 1), boron trifluoride, a strong Lewis acid, leads to β-lactone formation, whereas zinc acetate leads to formation of the polyester. Also, *n*-butylzinc and ethyl bromozinc acetate-when used as catalysts give as high a yield of polyester as does zinc acetate.

An interesting mechanistic possibility for this reaction involves the insertion of ketene into the zinc catalyst to form a zinc alkyl compound.[7] The zinc alkyl could then add to a molecule of aldehyde, as in the Reformatsky reaction, to give a zinc alkoxide. Insertion of ketene into the zinc alkoxide would re-form a zinc alkyl species which could continue the polymerization.[8]

Experimental Section

Boiling points are uncorrected. The ir spectra were obtained with a Baird-Atomic Model AB-2 spectrometer using sodium chloride cells. Nmr spectra were determined at 60 MHz with Varian Associates A-60 spectrometers. Field position values are recorded in parts per million relative to tetramethylsilane as an internal standard. Nmr peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), and m (multiplet). Mass spectra were recorded on an AEI Model MS 902 spectrometer. Molecular weights were determined by vapor phase osmometry by European Research Associates, Union Carbide Corp.

Poly(3-hydroxy-4-hexenoic acid) (1).—To a 5-l. four-necked reaction flask equipped with a stirrer, thermometer, condenser, and ketene diffuser were added crotonaldehyde (1260 g, 18.0 mol), toluene (2400 cc), and zinc isovalerate (13.5 g). Ketene (662 g, 15.7 mol) was added over a period of 6 hr while the temperature was maintained at 25°. During this time only 3 g of ketene came through the reaction zone unchanged. The reaction mixture was purged with nitrogen for 15 min, then stripped of solvent and excess crotonaldehyde under vacuum. The polyester, obtained as a residue from the distillation, weighed 1576 g (90% based on ketene): mol wt, 1200; ir (neat) 5.75 (C=O), 8.06 (COOC), and 10.43 μ (C=C); nmr (CDCl₃) 1.68 (d, 3, J = 6 Hz, CHCH₃), 2.61 (d, 2, J = 7 Hz, CH₂CO), and 5.6 ppm (m, 3).

Reduction of 1.—To a stirred suspension of lithium aluminum hydride (10.6 g) in ethyl ether (650 cc) was added a solution of **1** (50 g) in ethyl ether (250 cc) at a rate such that gentle reflux was maintained. After complete addition, the mixture was stirred for 2 hr, then quenched with water (25 cc). The ether solution was clarified by filtration, dried over magnesium sulfate, and distilled through a 7-in. glass helix column to give 32 g (62%) of 4-hexene-1,3-diol: bp 82–85° (1 mm); ir (neat) 2.9 (O–H) and 5.92 μ (C=C); nmr (CDCl₃) 1.72 (d, 3, J = 4 Hz, CH₃), 1.70 (m, 2, CH₂), 3.69 (t, 2, J = 5 Hz, CH₂OH), 4.20 (m, 1, CHOH), 4.52 (s, 2, OH), and 5.56 ppm (m, 2, HC=CH). The mass spectrum of this material possessed a parent molecular ion at *m/e* 116.0833 (C₆H₁₂O₂ required 116.0837).

Anal. Calcd for C₆H₁₂O₂: C, 62.07; H, 10.35. Found: C, 62.30; H, 10.38.

(7) For similar reactions, see L. C. Willemsens and G. J. M. van der Kerk, *J. Organometal. Chem.*, **4**, 241 (1965); I. F. Lutsenko, V. L. Foss, and N. L. Ivanova, *Dokl. Akad. Nauk SSSR*, **141**, 1270 (Engl) (1961).

(8) M. F. Lappert and B. Prokai, *Advan. Organometal. Chem.*, **5**, 242 (1967).

4-Hexene-1,3-diol.—Ethyl 3-hydroxy-4-hexenoate was prepared in 60% yield by the Reformatsky reaction of ethyl bromozinc acetate with crotonaldehyde under the conditions described by Fischer and Löwenberg.[9] The hydroxy ester (26 g, 0.16 mol) was reduced with lithium aluminum hydride (5.95 g, 0.156 mol) in ethyl ether giving 15 g (79%) of 4-hexene-1,3-diol, bp 80–85° (2 mm). The sample was identical (vpc, ir, nmr) with that obtained above. The mass spectrum of this material possessed a parent molecular ion at *m/e* 116.0840 (C₆H₁₂O₂ required 116.0837).

Attempted Preparation of 2.—A four-necked 500-cc reaction flask equipped with a stirrer, thermometer, condenser, diffusion tube, and dropping funnel was charged with dry toluene (250 cc) and boron trifluoride etherate (4 cc). To this was simultaneously added ketene (60 g, 1.4 mol) and crotonaldehyde (70 g, 1.0 mol); the temperature was maintained at −25°. After complete reaction, the catalyst was destroyed with sodium acetate (3.5 g), and the nmr spectrum of the cold solution was scanned. The nmr spectrum contained no absorption bands in the region between 3 and 4 ppm, the area in which hydrogens α to the carbonyl group of β-lactones absorb.

Preparation of 3.—The apparatus and procedure were the same as used in the attempted preparation of **2**. Acrolein (56 g, 1.0 mol) and ketene (59 g, 1.4 mol) were simultaneously added to the boron trifluoride solution at −25°. Destruction of the catalyst and distillation gave 71 g (72%) of **3**: bp 44–48° (4 mm) [lit.[6] bp 45–50° (3 mm)]; ir (neat) 5.4 (β-lactone C=O) and 8.0 μ (COOC); nmr (neat) 3.18 (dd, 1, C(=O)CH), 3.69 (dd, 1, C(=O)CH), 5.3 (m, 3), and 6.11 ppm (m, 1, O—CH).

Preparation of 4 in the Presence of 3.—A solution of acrolein (100 g), **3** (40 g), and zinc isovalerate (1 g) in benzene (150 cc) was charged into a four-necked 500-cc reaction flask equipped with a stirrer, thermometer, gas diffuser, and condenser. Ketene (70 g) was passed into the solution, but only a fraction of this (14 g) was absorbed. The reaction mixture was purged with nitrogen and distilled. Besides solvent and acrolein, there was obtained lactone **3** (27 g) and residue (22 g). Analysis of the nmr spectrum of the crude reaction mixture indicated that 36 g of **3** was present prior to distillation.

(9) F. G. Fischer and K. Löwenberg, *Chem. Ber.*, **66**, 669 (1933).

Routes to 2,19-Oxido-Δ⁴,⁶-3-keto Steroids

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Saturated 2,19-oxido-3-keto steroids have recently been prepared from the corresponding 2β-hydroxy-3α-acetates.[1] Attempts to convert these ketones into their conjugated analogs[1b] failed, however, and the steric deformation induced by the 2,19-oxide bridge has been made responsible for this. We wish to report the preparation of 2,19-oxido-4,6-dien-3-one (**13**) from 2-halo-19-acetoxy-Δ⁴,⁶-3-ketones **11** and **12** by hydrolysis and concomitant substitution of the halogen atoms in position 2 by the liberated 19-hydroxy group.

The synthesis commenced with 3β-acetoxy-5α-chloro-6,19-oxidoandrostan-17-one (**1**).[2] In view of the subsequent halogenating reactions planned, it appeared desirable to protect the oxygen function in position 17 by an ester group. The pivalate was chosen, as it

(1) (a) R. Kwok and M. E. Wolff, *J. Org. Chem.*, **28**, 423 (1963); (b) M. E. Wolff, W. Ho, and R. Kwok, *Steroids*, **5:1**, 1 (1964).

(2) J. Kalvoda, K. Heusler, H. Ueberwasser, J. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).