

Macrocyclic Dilactone. I. The Synthesis of 7-Hydroxyoctanoic Acid Dilactone

Noboru SUGIYAMA, Taketoshi GASHA and Choji KASHIMA

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo

(Received June 28, 1967)

In 1935, Stoll¹⁾ reported macrocyclic di- and trilactones as the by-products of monolactone synthesis by the azeotropic distillation of aliphatic ω -hydroxy carboxylic acid. It was further reported that the dilactone shows an anomalously higher melting point and less solubility in pentane than do mono- and trilactones. The method for obtaining macrocyclic dilactone by the depolymerization of the polyester of ω -hydroxy carboxylic acid was first found by Carothers²⁾ and has recently been improved by Dale.³⁾ This method consisted of the heating of hydroxy acid over 250°C for several hours. Both methods, azeotropic distillation and depolymerization, are difficult to control in order to obtain a desired mono-, di-, tri- or higher lactone. By these methods, dilactones have been obtained only from aliphatic ω -hydroxy carboxylic acid, not from secondary hydroxy carboxylic acids.

In this paper, a new synthesis of dilactone from 7-hydroxyoctanoic acid (I), the aliphatic secondary carboxylic acid, will be described. From 2-acetylcyclohexanone⁴⁾ we prepared 7-oxooctanoic acid,⁴⁾ which was then reduced to I by sodium borohydride. The infrared absorption spectrum of I shows the characteristic bands of hydroxyl and carboxyl groups. The bromination of I with phosphorus tribromide gave 7-bromooctanoic acid (II).⁶⁾

The hydroxyl bands disappeared in the infrared absorption spectrum of II. By the action of thionyl chloride, II gave the acid chloride (III), which was then treated with I to produce the dimeric ester, 6'-carboxy-2'-heptyl 7-bromooctanoate (IV). The infrared absorption spectrum of IV shows the absorption bands of carboxyl and ester carbonyl groups. By the high-dilution method,⁷⁾ IV cyclized to 7-hydroxyoctanoic acid dilactone (V) in the presence of potassium carbonate. The infrared absorption spectrum shows the absorption bands characteristic of the ester carbonyl group and no absorption bands of the carboxyl group. One gram of V was obtained from 13.4 g of I. The dilactone synthesized by this method is easy to purify, for the product is contaminated with neither mono- nor trilactone.

On the other hand, the heating of I at 250°C for 5 hr gave a polyester which showed ester carbonyl bands and no carboxyl bands in its infrared absorption spectrum. This polyester was depolymerized at 270°C in the presence of magnesium chloride. From the depolymerization product, V was isolated. By this depolymerization method, one gram of V was obtained from 100 g of I.

These facts suggest that, for the preparation of the macrocyclic dilactone from the secondary hydroxy carboxylic acid, the new method through the dimeric ester is superior to the depolymerization method. Moreover, the new method can be used to prepare the dilactone from hydroxy carboxylic acid with various functional groups, such as carbonyl and/or a double bond.

When different kinds of hydroxy carboxylic acids

1) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **18**, 1087 (1935).

2) E. W. Spanagel and W. H. Carothers, *J. Am. Chem. Soc.*, **58**, 654 (1936).

3) J. Dale, *J. Chem. Soc.*, **1965**, 72.

4) S. Hünig, E. Benzing and E. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

5) S. Hünig, E. Lücke and E. Benzing, *ibid.*, **91**, 129 (1958).

6) E. J. Lease and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 806 (1933).

7) J. Plesček, *Collection Czech. Chem. Commun.*, **22**, 49 (1957).

are employed, mixed dilactones will be prepared. The details of the preparation of the mixed dilactones will be discussed in another article.

Experimental

7-Hydroxyoctanoic Acid (I). To a solution of 21 g of 7-oxooctanoic acid in 12% aqueous sodium hydroxide, 3 g of sodium borohydride were added. The mixture was then kept for one hour at 75°C. After the addition of 18 g of sodium hydroxide, the reaction mixture was kept at this temperature for three hours, cooled to 5°C, acidified with hydrochloric acid, and extracted with ether. The ether solution was dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was distilled to give 13.2 g of I, bp 158—160°C/4 mmHg.

IR: 3400 (ν_{OH}), 1705 ($\nu_{\text{C=O}}$), 1270, 1130, 1100, 940 cm^{-1} .

The ethyl ester of I was identified by means of a comparison with an authentic sample.

7-Bromooctanoic Acid (II). To 5 g of I in anhydrous chloroform, 4.3 ml of phosphorus tribromide were slowly added at 0°C. After stirring for 2 hr at 0°C, the mixture was refluxed for 2 hr with continuous stirring. The mixture was then poured into ice water and extracted with ether. The ether solution was dried over anhydrous sodium sulfate. By distillation, 2.5 g of II was obtained; bp 115—125°C/4 mmHg.

IR: 1700 ($\nu_{\text{C=O}}$), 1280, 970, 930 cm^{-1} .

The ester of II was obtained and identified by means of a comparison with an authentic sample.

7-Hydroxyoctanoic Acid Dilactone (V). By the *Cyclization of the Dimeric Ester (IV)*. A mixture of 2.5 g of II and 10 ml of thionyl chloride in 20 ml of anhydrous benzene was refluxed for 2 hr. After the benzene and the excess thionyl chloride had been removed, the residue was distilled to afford 2 g of III, bp 133—138°C/20 mmHg.

IR: 1800 ($\nu_{\text{C=O}}$), 970 cm^{-1} .

A mixture of 2 g of III and 1.7 g of I in 15 ml of anhydrous benzene was refluxed for 5 hr. After washing with water, the benzene solution was dried over anhydrous sodium sulfate. By the evaporation of benzene, a residue that showed three spots on silica-gel thin-layer chromatography was obtained. The

residue was passed through a silica-gel (Merck 7729) column with a benzene-ethyl acetate (4:1 v/v) mixture; the second fraction was then collected, 1.7 g of IV being obtained.

IR: 1730 ($\nu_{\text{C=O}}$, ester), 1705 ($\nu_{\text{C=O}}$, acid), 1280, 1180, 970, 940 cm^{-1} .

NMR: 0.05 (1H, singlet, disappeared upon deuterium exchange), 5.18 (1H, multiplet), 6.57 (1H, multiplet), 7.78 (4H, multiplet), 8.29 (3H, doublet, $J=7$ cps), 8.56 (16H, multiplet), 8.83 τ (3H, doublet, $J=7$ cps). Over a period of 16 hr, a solution of 1.2 g of IV in 500 ml of methyl ethyl ketone was added to 10 g of anhydrous potassium carbonate suspended in 500 ml of methyl ethyl ketone under vigorous stirring and refluxing. The stirring and refluxing was continued for 7 hr after the addition. After the potassium carbonate had been filtered off, the filtrate was concentrated under reduced pressure, the residue was dissolved in ether, and the ethereal solution was washed with water and dried over anhydrous sodium sulfate. On removing of ether, the residue was chromatographed through a silica-gel (Merck 7734) column with a benzene-ethyl acetate (4:1 v/v) mixture. The pale yellow fraction was collected, 500 mg of V being obtained. The R_f value on silica-gel (Wakogel B-5) thin-layer chromatography with a benzene-ethyl acetate (1:1 v/v) mixture was 0.56.

Found: C, 66.92; H, 9.85%; mol wt (Rast), 312. Calcd for $\text{C}_{16}\text{H}_{28}\text{O}_4$: C, 67.56; H, 9.92%; mol wt, 284.4.

IR: 1730 ($\nu_{\text{C=O}}$), 1260, 1170 cm^{-1} .

NMR: 5.24 (2H, multiplet), 7.83 (4H, multiplet), 8.62 (16H, multiplet), 8.85 τ (6H, doublet, $J=6$ cps).

By the *Depolymerization Method*. When one gram of I was heated for 5 hr at 250°C the polyester was obtained.

IR: 1730 ($\nu_{\text{C=O}}$), 1165, 1180 cm^{-1} .

The polyester was depolymerized in the presence of 20 mg of magnesium chloride at 270°C for 5 hr under a pressure of 1 mmHg or less. The distillate was chromatographed through a silica-gel (Merck 7734) column with a benzene-ethyl acetate (4:1 v/v) mixture. The pale yellow fraction was afforded as a substance, which was identified with V by means of the R_f value shown by silica-gel thin-layer chromatography and by means of its infrared absorption spectrum; yield 10 mg