BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1937—1939 (1968)

Macrocyclic Dilactone. II. The General Synthesis of Macrocyclic Dilactone

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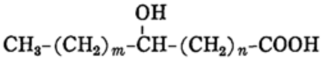
(Received February 19, 1968)

One previous papar reported the synthesis of 7-hydroxyoctanoic acid dilactone through the dimeric ester. This paper will describe how the dilactone of 12-hydroxystearic acid is synthesized by this method. The dilactone from two kinds of hydroxy alkanoic acid, 7-hydroxyoctanoic acid and 12-hydroxystearic acid, is also otained. From these results, it seems that this new method can be of general use in the synthesis of various kinds of dilactones.

Previously, the present authors reported on the preparation of the dilactone of 7-hydroxyoctanoic acid by two methods, the pyrolytic depolymerization of the polyester and the cyclization of the dimeric ester.[1] The latter method was found to be superior for the synthesis of 7-hydroxyoctanoic acid dilactone (I).

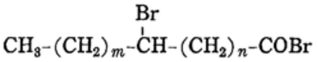
This paper will describe the synthesis of dilactone from 12-hydroxystearic acid (III), which can cyclize to a thirteen-membered monolactones from 12-hydroxystearic acid (III).

As a result of the action of thionyl bromide, III gave 12-bromostearoyl bromide (IV), which was then treated with the original acid III to produce the dimeric ester, 1′-carboxy-11′-heptadecyl 12-bromostearate (V). The infrared absorption spectrum of V showed absorption bands at 1730 and 1180 cm^{-1} of the ester carbonyl group. The NMR spectrum of V is shown in Table 1. These spectral data and the molecular weight measurment support the structure of V. By means of the high-dilution method in methyl ethyl ketone,[2] V was cyclized to 12-hydroxystearic acid dilactone, 1,14-dioxa-2,15-dioxo-13,26-dihexylcyclohexacosane (VI). The structre of VI was comfirmed as follows. The infrared absorption spectrum showed the ester carbonyl bands at 1730 and 1180 cm^{-1}, and no absorption in the region of carboxyl bands. The NMR spectrum, listed in Table 2, showed the multiplet at τ 5.16 of the methine protons at C-13 and C-26, the triplet at τ 7.79 of the methylene protones



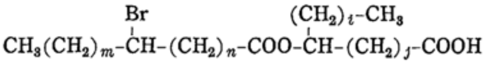
$$CH_3\text{-}(CH_2)_m\text{-}\overset{OH}{\overset{|}{C}}H\text{-}(CH_2)_n\text{-}COOH$$

II: $m=0,\ n=5$
III: $m=5,\ n=10$



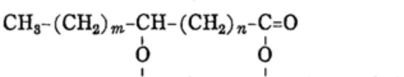
$$CH_3\text{-}(CH_2)_m\text{-}\overset{Br}{\overset{|}{C}}H\text{-}(CH_2)_n\text{-}COBr$$

IV: $m=5,\ n=10$
IX: $m=0,\ n=5$



$$CH_3(CH_2)_m\text{-}\overset{Br}{\overset{|}{C}}H\text{-}(CH_2)_n\text{-}COO\text{-}\overset{(CH_2)_i\text{-}CH_3}{\overset{|}{C}}H\text{-}(CH_2)_j\text{-}COOH$$

VIII: $i=m=5,\ i=n=10$
V: $i=m=5,\ j=n=10$
VII: $m=0,\ i=n=5,\ j=10$
XI: $i=m=0,\ j=n=5$



$$\begin{array}{l} CH_3\text{-}(CH_2)_m\text{-}CH\text{-}(CH_2)_n\text{-}C{=}O \\ \qquad\qquad\quad | \qquad\qquad\quad | \\ \qquad\qquad\quad O \qquad\qquad\quad O \\ \qquad\qquad\quad | \qquad\qquad\quad | \\ \qquad\quad O{=}C\text{—}(CH_2)_j\text{—}CH(CH_2)_i\text{-}CH_3 \end{array}$$

I: $i=m=0,\ j=n=5$
VI: $i=m=5,\ j=n=10$
X: $m=0, i=n=5, j=10$ or $i=0, j=m=5, n=10$

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[1] N. Sugiyama, T. Gasha and C. Kashima, This Bulletin, **40**, 2713 (1967).

[2] J. Plesek, *Collection Czech. Chem. Commun.*, **22**, 49 (1957).

TABLE 1. THE NMR SPECTRAL DATA OF V, VII, VIII AND XI (τ)

	V	VII	VIII	XI
Carboxyl	−0.05	1.50	−0.43	0.05
Methine (CH-O)	5.21	5.40	5.21	5.18
Methine (CH-Br)	5.91	6.02	6.00	6.57
Methylene (CH_2-C=O)	7.78	7.75	7.80	7.78
Methylene (CH_2-CBr)	8.10	8.34	8.10	—*
Methyl (CH_3CBr)	—	8.30	—	8.29
Methyl (CH_3-C-O)	—	—	8.85	8.83
Methyl (CH_3-CH_2)	9.11	9.12	9.09	—
Other methylenes	8.72	8.71	8.68	8.56

* The methylene (CH_2-CBr) signal was indistinguishable from the multiplet of other methylenes.

TABLE 2. THE IR AND THE NMR SPECTRAL DATA OF I, VII, AND X

	I	VI	X
$\nu_{C=H}$	1730	1730	1730
τ_{CH} (CH-O)	5.24	5.16	5.21
τ_{CH_2} (CH_2-C=O)	7.83	7.79	7.79
τ_{CH_3} (CH_3-C-O)	8.85	—	8.86
τ_{CH_3} (CH_3-CH_2)	—	9.12	9.14
τ_{CH_2} (other methylenes)	8.62	8.73	8.73

at C-3 and C-16, the triplet at τ 9.21 of the methyl protons, and multiplet centered at τ 8.73 of the methylene protons. The molecular weights and the results of the elemental analysis supported the structure of VI.

Using this new method, it is effected that a dilactone can be obtained from two kinds of hydroxy alkanoic acids. The dilactone which is formed from two kinds of hydroxy carboxylic acids can be called a mixed dilactone. The preparation of a mixed dilactone has not been found described in the literature except for the heating a miture of two kinds of acids; by this method the corresponding dilactone can not be selectively obtained. The present authors succeded in synthesizing the dilactone selectively from two kinds of acids, II and III. Since two kinds of ester are expected as the intermediates in the synthesis of the mixed dilactone, two synthetic routes were examined for obtaining the mixed dilactone from II and III. One route was the cyclization of 1′-carboxy-11′-heptadecyl 7-bromooctanoate (VII), and the other, that of 1′-carboxy-6′-heptyl 12-bromostearate (VIII).

The dimeric ester VII was obtained from 7-bromooctanoyl bromide (IX) by treatment with III. The structure of VII was confirmed as follows. The infrared absorption spectrum was similar to that of V; the NMR srectrum was as shown in Table 1. The molecular weight measurements and the elemental analysis supported the structure of VII. Similarly, the dimeric ester VIII was obtained from 12-bromostearoyl bromide (IV) by treatment of 7-hydroxyoctanoic acid (II). The infrared absorption spectrum was similar to that of VII, while the NMR spectrum was as listed in Table 1. The spectral data, the molecula weight measurements, and the elemental analysis showed the structure of the dimeric ester VIII.

By the high-dilution method,[2] VII was cyclized in the presence of potassium carbonate. The infrared absorption spectrum of this cyclized product showed ester carbonyl bands at 1730 and 1180 cm^{-1}, and no band characteristic of the carboxyl group. The NMR spectrum, listed in Table 2, showed the multiplet at τ 5.21 assigned to methine protons, the triplet at τ 7.79 of methylene protons, and the signals at τ 8.86 and 9.14 of methyl protons, while other protons appeared at τ 8.73 as a multiplet. The spectral data, the molecular weight measurements, and the elemental analysis confirmed this cyclized product to be the mixed dilactone, 1,14-dioxa-2,15-dioxo-13-hexyl-21-methylcycloheneicosane (X). Under the same conditions, catalyzed by potassium carbonate, VIII was cyclized, and the cyclized product was identified with X by the spectral data and by the R_f value on silicagel thin-layer chromatograpy.

In conclusion, these results suggest that the new synthetic method is generally applicable to the preparation of the dilactone from hydroxy alkanoic acids. Moreover, the mixed dilactones can be obtained from two different kinds of hydroxy alkanoic acids by this methods.

Experimental

1′-Carboxy-11′-heptadecyl 12-bromostearate (V). A mixture of 10 g of III and 10 m*l* of thionyl bromide in 100 m*l* of dry chloroform was refluxed for 3 hr with stirring. After the removal of the solvent and the excess thionyl bromide, the residue was dissolved in 100 m*l* of dry benzene, and then 9 g of III was added. The mixture was refluxed for 4 hr with stirring, and then washed with water and dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue, which showed three spots on silica-gel thin-layer chromatography, was passed through a silica-gel (Merck 7734) column with a benzene - chloroform (7 : 3 v/v) mixture. When the second fraction was then collected, 8.5 g of V were obtained, mp 55°C.

Found: C, 66.95; H, 10.68%; mol wt (titration), 625. Calcd for $C_{36}H_6O_4Br$: C, 66.93; H, 10.79%; mol wt, 645.97. IR (liquid film): 3500—2400, 1730, 1710, 1180 and 970 cm^{-1}.

1, 14-Dioxa-2, 15-dioxo-13, 26-dihexylcyclohexacosane (VI). Over a 28 hr-period, a solution of 2.5 g of V in 50 m*l* of methyl ethyl ketone was added, through a reflux condenser, to 600 m*l* of methyl ethyl ketone containing 15 g of anhydrous potassium carbonate under vigorous stirring and refluxing. After the additon of V, the stirring and refluxing were continued for 8 more hours. The reaction mixture was concentrated after the removal of potassium carbonate, and the residue was dissolved in ether. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was passed through a silica-gel (Merck 7729) column with a benzene-ethyl acetate (4 : 1 v/v) mixture. The first fraction was then collected, and the solvent was removed. The first fraction was then collected, and the solvent was removed. The residue was chromatographed on an alumina (Wako alumina) column with a benzene-ethyl acetate (20 : 1 v/v) mixture. A fraction which showed a R_f value of 0.60 on silica-gel (Wakogel B-5) thin-layer chromatograph with a benzene-ethyl acetate (10 : 1 v/v) mixture was then collected ; yield 1 g.

Found: C, 76.92; H, 12.27%; mol wt (Rast), 619. Calcd for $C_{36}H_{68}O_4$: C, 76.54; H, 12.13%; mol wt, 564.90. IR (liquid film): 2940, 2860, 1730, 1460, 1180 and 1110 cm^{-1}.

1′-Carboxy-11′-heptadecyl 7-Bromooctanoate (VII). A mixture of 4 g of II and 6 m*l* of thionyl bromide in 100 m*l* of dry benzene was refluxed for 3.5 hr with stirring. After the removal of the solvent and the excess thionyl bromide, the residue was distilled under reduced pressure, bp 146—150°C/10 mmHg, 2.1 g of IX were thus obtained. IR (liquid film): 2940, 2860, 1800, 1460 and 970 cm^{-1}. The mixture of 2.1 g IX and 3 g of III in 50 m*l* of dry chloroform was refluxed for 3 hr with stirring. The reaction mixture was then treated by the same procedure as V. Four grams of VII were then obtained by recrystallization from chloroform; mp 65°C.

Found: C, 61.84; H, 9.88%; mol wt (titration), 494. Calcd for $C_{26}H_{49}O_4Br$: C, 61.81; H, 9.72%; mol wt, 505.67. IR (liquid film): 3500—2400, 1730, 1710, 1470, 1190 and 970 cm^{-1}.

1′-Carboxy-6′-heptyl 12-Bromostearate (VIII). 12-Bromostearoyl bromide, which had been obtained from 10 g of III and 10 m*l* of thionyl bromide, was added to a solution of 3.5 g of II in 100 m*l* of dry benzene, after which the mixture was refluxed for 4.5 hr with stirring. The reaction mixture was then treated by the same procedure as were V and VII; 1.5 g of VIII were thus obtained.

Found: C, 61.59; H, 10.14%; mol wt (titration), 594. Calcd for $C_{26}H_{49}O_4Br$: C, 61.81; H, 9.72%; mol wt, 505.67. IR (liquid film): 3500—2400, 1730, 1710, 1460, 1180 and 970 cm^{-1}.

1,14-Dioxa-2,15-dioxo-13-hexyl-21-methylcycloheneicosane (X). For 20 hr, a solution of 1 g of VII in 50 m*l* of methyl ethyl ketone was slowly added, under vigorous stirring and refluxing, through a reflux condenser to 600 m*l* of methyl ethyl ketone containing 15 g of anhydrous potassium carbonate. After continuous stirring and refluxing for 4 hr, the reaction mixture was treated by the same procedure as VI. The yield of X was 0.5 g; the R_f value on silica-gel (Wokogel B-5) thin-layer chromatography with a benzene-ethyl acetate (10 : 1 v/v) mixture was 0.53.

Found: C, 72.68; H, 11.19%; mol wt (Rast), 422. Calcd for $C_{26}H_{48}O_4$: C, 73.53; H, 11.39%; mol wt, 424.64. IR (liquid film); 2940, 1730, 1460, 1180 and 1110 cm^{-1}.

X was also obtained by the cyclization of VIII by the same procedure; it was identified by means of the infrared absorption, the NMR spectra, and the R_f value of thin-layer chromatography.

NMR Spectra. The NMR spectra were measured on a Hitachi H-60 High resolution Nuclear Magnetic Resonance Spectrometer. The solvent was carbon tetrachloride, while tetramethylsilane was used as the internal standard.