Studies on Phenolic Lactones

Part III. Synthesis of ($\pm$) Hibalactone

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($\pm$) Hibalactone, α -piperonylidene- β -piperonyl-butyrolactone, was synthesized by the following method. α -Piperonylidene- β -piperonyl-succinic acid dimethylester was reduced with lithium aluminum hydride to 2-piperonylidene-3-piperonyl-1, 4-butanediol, m. p. 117°C. Oxidation of the glycol with manganese dioxide in acetone yielded α -piperonylidene- β -piperonyl- γ -hydroxy-butyraldehyde, which afforded racemic hibalactone, m.p. 154~5°, after oxidation with silver oxide and lactonization.

In the previous paper the authors reported the synthesis of isohibalactone, the geometric isomer of hibalactone, by two methods; (1) reduction of α -piperonylidene- β -piperonyl-succinic acid β -thioethyl α -methyl ester with Raney nickel catalyst¹⁾, (2) condensation of piperonal with β -

piperonyl-butyrolactone²⁾. Authors devised the other method for synthesizing α -piperonylidene- β -piperonyl-butyrolactone, and synthesized racemic hibalactone as follows:

The condensation of piperonal and dimethyl piperonyl-succinate with sodium ethylate af-

forded α -(3,4-methylenedioxyphenyl)-hydroxy-methyl)- β -(3,4-methylenedioxybenzyl)-succinic acid (I). Methylation of the hydroxy acid with diazomethane yielded hydroxyester (II), m.p. 87~8°C. When the hydroxyester was treated with phosphorus tribromide in the presence of pyridine, the product was α -piperonylidene- β -

1) K. Yamashita and M. Matsui, This Bulletin, 22, 277 (1958).

2) K. Yamashita and M. Matsui, This Bulletin, 23, 230 (1959).

piperonyl-succinic acid dimethylester (III), m.p. $83\sim 4^{\circ}\text{C}$, and not bromoester. Reduction of dimethyl ester (III) with lithium aluminum hydride afforded 2-piperonylidene-3-piperonyl-1, 4-butanediol (IV), m.p. 117°C . When this glycol was treated with precipitated manganese dioxide powder in acetone the hydroxymethyl group adjacent to double bond was oxidized to aldehyde group and α -piperonylidene- β -piperonyl- γ -hydroxy-butyraldehyde (V) was obtained. Oxidation of the aldehyde with silver oxide in alkaline solution afforded hibalactonic acid (VI), m.p. $143\sim 4^{\circ}\text{C}$, and lactonization with hydrochloric acid afforded racemic hibalactone (VII), m.p. $154\sim 5^{\circ}\text{C}$. The lactone showed good agreement in infrared spectrum and ultraviolet spectrum with authentic (–)hibalactone.

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EXPERIMENTAL

All melting points were observed value only.

α -(3,4-Methylenedioxyphenyl-hydroxymethyl)- β -(3,4-methylenedioxybenzyl)-succinic acid dimethylester (II).

α -(3,4-Methylenedioxyphenyl-hydroxymethyl)- β -(3,4-methylenedioxybenzyl)-succinic acid¹⁾, 13 g, was suspended in 50 ml of ether and esterified with ethereal solution of diazomethane prepared from 10 g of nitrosomethylurea. Evaporation of solvent left 13.5 g of ester, m.p. $85\sim 7^{\circ}\text{C}$. After recrystallization from methanol, its melting points rose to $87\sim 8^{\circ}\text{C}$. *Anal.* Found: C, 60.74; H, 5.08. Calcd. for $\text{C}_{22}\text{H}_{22}\text{O}_8$: C, 61.4; H, 5.1%.

α -Piperonylidene- β -piperonyl-succinic acid dimethyl ester (III).

α -(3,4-Methylenedioxyphenyl-hydroxymethyl)- β -(3,4-methylenedioxybenzyl)-succinic acid dimethyl ester, 13 g, was dissolved in 30 ml of benzene and 0.12 g of pyridine was added. To a solution of 2.95 g of phosphorus tribromide in 50 ml of benzene, 0.5 g of pyridine was added and the above ester solution was added dropwise with stirring in the cold. After refluxing 2 hours, the reaction mixture was poured onto ice and extracted with ether. After washing twice with water, evaporation of the solvent from ethereal extract left 12 g of α -piperonylidene- β -piperonyl-succinic acid dimethyl

ester, m.p. $83\sim 4^{\circ}\text{C}$. Recrystallization from ethyl acetate-petroleum benzene afforded colorless needles, m.p. $84\sim 5^{\circ}\text{C}$. *Anal.* Found: C, 63.96; H, 4.66. Calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_8$: C, 64.1; H, 4.8%.

2-Piperonylidene-3-piperonyl-1, 4-butanediol (IV).

A solution of 11 g of dimethyl α -piperonylidene- β -piperonyl-succinate in 200 ml of dry ether was added dropwise to a suspension of 1.3 g of lithium aluminum hydride in 50 ml of anhydrous ether at a rate so as to produce gentle reflux. After refluxing for an hour, the excess hydride was destroyed by careful addition of ethyl acetate and water. With stirring 40 ml of 15% hydrochloric acid was slowly added. The ether layer was separated and the solvent was removed by distillation under atmospheric pressure. The residual oil was refluxed with 50 ml of 5% methanolic potash for an hour to destroy any unreacted ester. After the addition of 50 ml of water, methanol was distilled off and glycol was extracted with ether. Evaporation of ether left 8.9 g of oily glycol, which gradually solidified, m.p. $108\sim 9^{\circ}\text{C}$. Recrystallization from ethanol gave colorless needles, m.p. $115\sim 7^{\circ}\text{C}$. *Anal.* Found: C, 66.51; H, 5.18. Calcd. for $\text{C}_{20}\text{H}_{20}\text{O}_6$: C, 67.4; H, 5.6%.

($\pm$)-Hibalactone.

To a solution of the glycol, 8.9 g, in 150 ml of acetone precipitated manganese dioxide powder (35 g) was added and left standing for 24 hours with occasional shaking. Manganese dioxide was filtered and washed with acetone, and the combined filtrate was concentrated to syrup. α -Piperonylidene- β -piperonyl- γ -hydroxy-butyraldehyde was obtained as a oily residue, weighed 8.0 g. Chloroform could be used in place of acetone but acetone was more preferable as the solvent.

The crude aldehyde (8.0 g) was dissolved in 50 ml of warm ethanol and 80 ml of 5% sodium hydroxide was added. Silver oxide freshly precipitated from 8.0 g of silver nitrate was added and warmed for an hour

FIG. 1. Ultraviolet Absorption Spectra of Hibalactone.

— Synthetic ($\pm$) Hibalactone
 --- Authentic (–) Hibalactone

FIG. 2. Infrared Absorption Spectra of Hibalactone.

(I) Authentic (–) Hibalactone
 (II) Synthetic (±) Hibalactone

with vigorous stirring. The hot mixture was filtered and after the addition of 100 ml of water ethanol was distilled off. Upon cooling the sparingly soluble sodium salt of hibalactonic acid was precipitated gradually. After the removal of neutral substances with chloroform extraction, the aqueous solution was acidified with hydrochloric acid and warmed on water bath for 30 minutes. The reaction mixture was carefully poured into excess of sodium bicarbonate solution and extracted three times with chloroform. The combined extract was washed with water and dried over sodium sulfate. After evaporation of chloroform the residual mass was dissolved in 100 ml of hot ethanol and cooled in refrigerator. The precipitated crude hibalactone was collected by filtration and recrystallized from methanol, yielded 3.1 g, m.p. 154°C. *Anal.* Found: C, 67.52; H, 4.81. Calcd. for

$C_{20}H_{16}O_6$: C, 68.1; H, 4.5%.

Upon admixture with isohibalactone, m.p. 156°C, the melting point depressed to 140~2°C. The infrared absorption spectrum and ultraviolet spectrum of this lactone agreed completely with authentic (–) hibalactone

(±)-Hibalactonic acid.

(±)-Hibalactone (1.0 g) was boiled with 10 ml of 1 N-NaOH and 20 ml of ethanol for 10 minutes, and the clear solution diluted with water. On cooling the sparingly soluble sodium salt precipitated as colorless leaflets, m.p. 108~9°C. The mixture was chilled in ice, and acidified with acetic acid. The product (0.9 g) which was collected after several hours and dried in vacuo, formed colorless felt-like needles, m.p. 143~4°C. *Anal.* Found: C, 64.99; H, 4.94. Calcd. for $C_{20}H_{16}O_7$: C, 64.9; H, 4.8%.