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115. **Yoshikata Kuwayama** : Studies on the Use of γ-Butyrolactone. VI.[*1] A New Synthesis of Dihydrodictamnine.

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Dihydrodictamnine has already been obtained by hydrogenation[1] of dictamnine or by synthesis by several workers.[2~4]

In the present work, dihydrodictamnine was synthesized in a fairly good yield from 2-acetyl-γ-butyrolactone by the route shown in Chart 1.

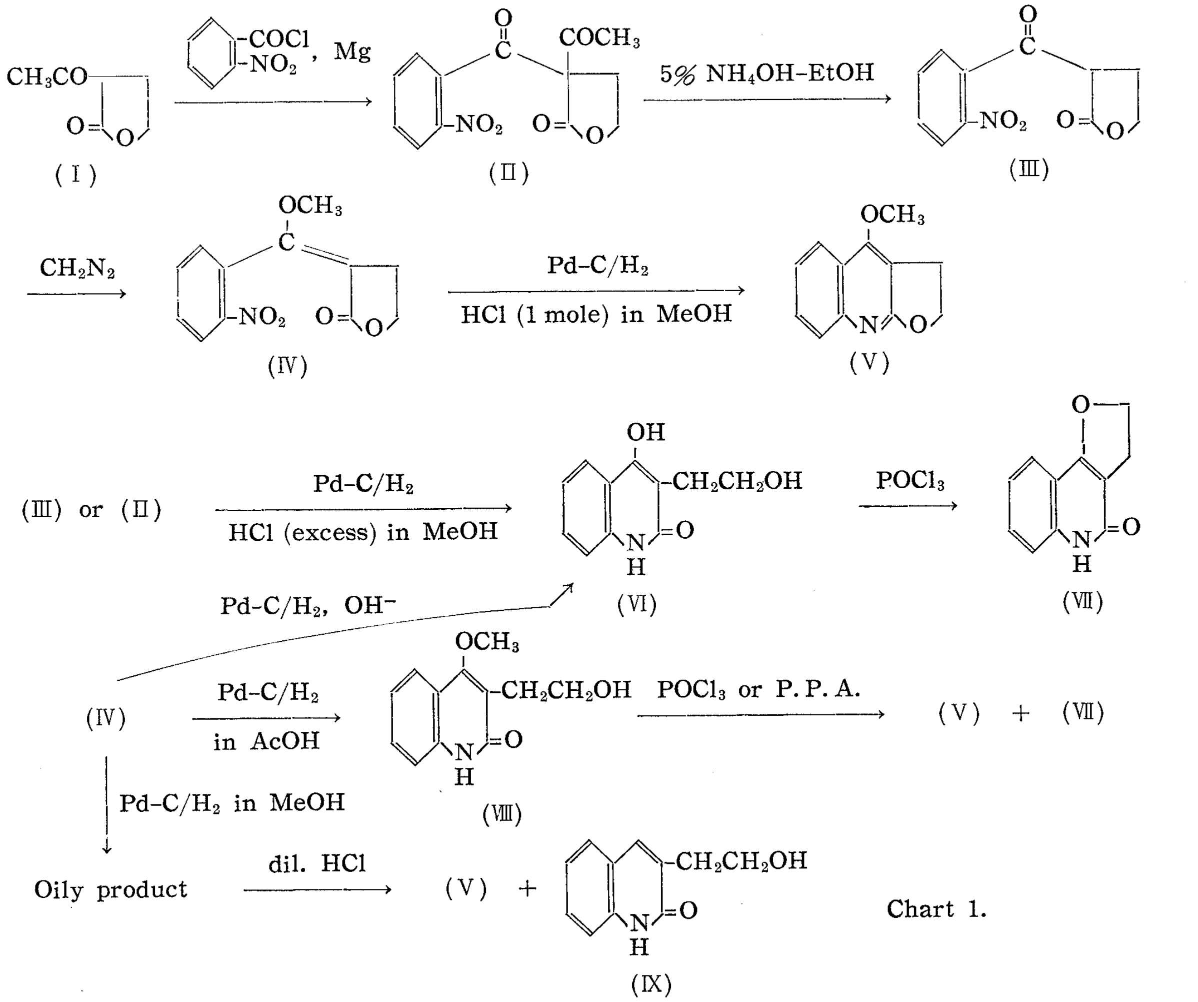

Chart 1.

In accordance with Viscontini's β-ketoester synthesis[5], 2-acetyl-2-(*o*-nitrobenzoyl)-γ-butyrolactone (II) was prepared by condensation of acetylbutyrolactone (I) and *o*-nitrobenzoyl chloride with magnesium ethoxide and 2-(*o*-nitrobenzoyl)-γ-butyrolactone (III) was prepared by deacetylation of (II) with ethanolic ammonia. (III) yielded 4-hydroxy-3-(2-

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[*1] Part V. Y. Kuwayama : Yakugaku Zasshi, (1961) to be published.

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1) T. Ota, T. Miyazaki, Y. Mori : Yakugaku Zasshi, **74**, 708 (1954).

2) T. Sato, M. Ota : Bull. Chem. Soc. Japan, **30**, 708 (1957).

3) M. F. Grundon, N. J. McCorkindale : J. Chem. Soc., **1957**, 2177.

4) R. G. Cooke, H. F. Haynes : Australian J. Chem., **11**, 225 (1958).

5) M. Viscontini, N. Merckling : Helv. Chim. Acta, **35**, 2280 (1952).

hydroxyethyl)carbostyril (VI) on being reduced over palladium-carbon catalyst in methanolic hydrochloric acid. (II) also was converted into (VI) by the same reduction.

(VI) was reacted with phosphoryl chloride on a steam-bath and gave colorless needles (VII), m.p. 280~281°, which would be identical with 2,3-dihydro-5*H*-furo[3,2-*c*]quinolin-4-one prepared by Grundon, *et al.*,⁶⁾ because (VII) was insoluble in dilute alkali and agreed in melting point, analytical values, and spectral data of ultraviolet and infrared absorptions in the literature.

The above results suggest that the reduction of the enol-methyl ether of (III) would form 4-methoxycarbostyril derivative, which would be expected to cyclize to linear furoquinoline under suitable condition to prevent the opening of the lactone-ring.

(III) treated with diazomethane in ether gave 2-(α-methoxy-*o*-nitrobenzylidene)-γ-butyrolactone (IV). The reduction of nitro group in (IV) was experimented in various media to effect ring-closure into dihydrodictamnine and successful result, as shown in Table I, was obtained by the following method. Reduction of (IV) in methanol over palladized charcoal, at ordinary pressure in the presence of an equivalent amount of hydrochloric acid, gave a base (V), m.p. 104~105°, in a good yield. Admixture of this base with dihydrodictamnine synthesized by Cooke showed no depression of the melting point.

TABLE I. Reduction of (IV)

Medium (cc.)	from 0.5 g. of (V)	
	Product	Yield (g.)
(1) 0.5*N* HCl 4: MeOH 25	(V)	0.35
(2) 0.5*N* HCl 8: MeOH 25	(V) (VIII)	0.1; 0.2
(3) AcOH 30	(VIII)	0.37
(4) MeOH 30	oily product	
(5) 1*N* NH_4OH 2: MeOH 25	(VI)	0.3
(6) 1*N* NaOH 2: MeOH 25	(VI)	0.25

By addition of more than an equivalent amount of hydrochloric acid this reduction yielded 4-methoxy-3-(2-hydroxyethyl)carbostyril (VIII) as a by-product besides dihydrodictamnine. Furthermore, in the reduction of (IV) in acetic acid solution, only (VIII) was produced. In the reduction in neutral medium, (IV) yielded an oily substance which separated into (V) and 3-(2-hydroxyethyl)carbostyril (IX)⁷⁾ after treatment with dilute hydrochloric acid. The basic reduction of (IV) gave (VI) in a good yield. It was considered that the methoxyl group of (IV) was hydrolyzed in a basic medium.

Dihydrodictamnine was also obtained from (VIII) in company with (VII) on warming it with phosphoryl chloride or polyphosphoric acid on a steam bath.

Experimental

2-Acetyl-2-(*o*-nitrobenzoyl)-γ-butyrolactone (II)——According to Viscontini's method: To a stirred solution of 100 cc. of dehyd. Et_2O, 3 g. of Mg, 20 cc. of dehyd. EtOH, 1.2 cc. of dehyd. CCl_4, and 15 g. of (I), a solution of 20 g. of *o*-nitrobenzoyl chloride in dehyd. Et_2O was added slowly. After the reaction mixture was allowed to stand at room temperature overnight, it was acidified with 10% H_2SO_4 and separated crystals were recrystallized from MeOH, forming colorless prisms of m.p. 117~119°; yield, 23 g. *Anal.* Calcd. for $C_{13}H_{11}O_6N$: C, 56.32; H, 4.00; N, 5.05. Found : C, 56.72; H, 4.01; N, 5.05.

2-(*o*-Nitrobenzoyl)-γ-butyrolactone (III)——5 g. of (II) was added into 30 cc. of 5% NH_4OH-EtOH with shaking. After the clear solution was allowed to stand at room temperature overnight, it was acidified with 10% H_2SO_4 and separated crystals were purified from MeOH, forming colorless prisms of m.p. 75~76°; yield, 2.4 g. *Anal.* Calcd. for $C_{11}H_9O_5N$: C, 56.17; H, 3.86; N, 5.96. Found : C, 56.24; H, 3.92; N, 5.92.

2-(α-Methoxy-*o*-nitrobenzylidene)-γ-butyrolactone (IV)——A solution of 1 g. of (III) in 100 cc. of Et_2O with CH_2N_2, prepared from 4 g. of N-methyl-N-nitrosourea by the usual method, was allowed

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6) M. F. Grundon, N. J. McCorkindale, M. N. Rodger : J. Chem. Soc., **1955**, 4284.

7) Y. Kuwayama : Yakugaku Zasshi, **81**, 1278 (1961).

to stand in an ice-box for 3 days. The separated solid was recrystallized from MeOH, forming light yellow prisms of m.p. 135～137°; yield, 0.8 g. *Anal.* Calcd. for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.45; N, 5.62. Found : C, 58.01; H, 4.51; N, 5.60.

Dihydrodictamnine (V)——A solution of 0.5 g. of (IV) in 25 cc. of MeOH, added with 4 cc. of 0.5*N* HCl was reduced over Pd-C (prepared from 2 cc. of 1% $PdCl_2$ solution and 0.2 g. of charcoal) at ordinary pressure. After 140 cc. (at 17°) of H_2 was absorbed, the solution was concentrated in vacuum and neutralized with 10% NH_4OH. The separated solid was collected, dried, and recrystallized from benzene-benzine to colorless needles of m.p. 104～105°. Admixture of this product with dihydrodictamnine synthesized by Cooke melted at 104～105°. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found : C, 71.88; H, 5.53; N, 6.93.
Picrate : Yellow needles (from MeOH), m.p. 184～186°. *Anal.* Calcd. for $C_{18}H_{14}O_9N_4$: C, 50.24; H, 3.28; N, 13.02. Found : C, 50.32; H, 3,32; N, 13.20.

4-Hydroxy-3-(2-hydroxyethyl)carbostyril (VI)——a) A mixture of 0.5 g. of (II), 30 cc. of MeOH, and Pd-C (prepared from 2 cc. of 1% $PdCl_2$ solution and 0.1 g. of charcoal) was reduced in H_2 atmosphere. After absorption of H_2 (150 cc. at 17°) had ceased, the solvent was evaporated in a diminished pressure and the crystals obtained were purified from MeOH, forming colorless needles of m.p. 250～251°; yield, 0.37 g. This was soluble in 10% NH_4OH and colored dark red with $FeCl_3$. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found : C, 64.26; H, 5.30; N, 6.60.
b) 1.5 g. of (III) was treated similarly as described above and gave colorless needles of m.p. 250～251° (from EtOH); yield, 0.25 g. Admixture with (VI) melted at 250～251°.

Reduction of (IV) in Various Media——A solution of 0.5 g. of (IV) in various media indicated in Table I was reduced with H_2 over Pd-C (prepared from 2 cc. of 1% $PdCl_2$ solution and 0.2 g. of charcoal) as described for dihydrodictamnine. The solution was concentrated in vacumm and after-treatment of the residue was carried out as follows : a) Addition of excess HCl : After the residue was neutralized with 10% NH_4OH, the separated solid was collected, dried, and extracted with Et_2O. The crystals obtained from the extract were identified with dihydrodictamnine by admixture. Extracted residue with Et_2O was crystallized from benzene to colorless prisms of m.p. 176～177°. *Anal.* Calcd. for $C_{12}H_{13}O_3N$ (4-methoxy-3-(2-hydroxyethyl)carbostyril) : C, 65.75; H, 5.98; N, 6.39. Found: C, 65.74; H, 5.98; N, 6.30. IR $\lambda_{\max}^{\mathrm{KBr}}$ 1634 cm^{-1} (2-quinolone, strong).
b) In AcOH solution : After the residue was basified with 10% NH_4OH, the separated solid was recrystallized from benzene to colorless prisms of m.p. 176～177°. Its admixture with 4-methoxy-3-(2-hydroxyethyl)carbostyril (VIII) showed no depression.
c) In neutral medium : The residue did not crystallize. The residue was dissolved in 5 cc. of 5% HCl, basified with 5% NH_4OH, and the separated solid was collected and extracted with Et_2O. The extract gave 0.1 g. of (V), after evaporation of Et_2O. The extracted residue was recrystallized from MeOH, forming colorless needles of m.p. 195～197°; yield, 0.1 g. Admixture of this with 3-(β-hydroxyethyl)carbostyril⁷⁾ showed no depression.
d) In basic medium : After the residue was acidified with 20% AcOH solution, the separated solid was recrystallized from MeOH to colorless needles of m.p. 250～251°. Admixture of this with (VI) showed no depression.

2,3-Dihydro(5*H*)furo[3,2-c]quinolin-4-one (VII)——A solution of 0.5 g. of (VI) dissolved in 5 cc. of $POCl_3$ was warmed on a steam bath at 60～70° for 1 hr. The mixture was poured into ice-water and separated crystal was purified from MeOH to colorless needles of m.p. 280～281°, which agreed with melting point in the literature,⁶⁾ yield, 0.3 g. *Anal.* Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found : C, 70.57; H, 4.78; N, 7.77. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : 231 (4.45), 290 (3.89), 315 (3.87). IR: $\lambda_{\max}^{\mathrm{KBr}}$ 1660 cm^{-1} (2-quinolone, strong).

Reaction of (VIII) with $POCl_3$ or Polyphosphoric Acid——A solution of 0.5 g. of (VIII) dissolved in 5 cc. of $POCl_3$ or polyphosphoric acid (prepared from 100 cc. of 85% H_3PO_4 and 100 g. of P_2O_5) was warmed at 80° on a steam bath for 30 min. After cool, the mixture was poured into ice-water, separated crystals were collected, dried, and purified from MeOH; m.p. 280～281°; yield, 0.05 g. Admixture with (VII) melted at 280～281°. The filtrate was neutrallized with Na_2CO_3 and (V) precipitated, m.p. 104～105° (from benzene-benzine); yield, 0.1 g.

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Summary

Dihydrodictamnine was prepared in a fairly good yield by the catalytic reduction of 2-(α-methoxy-*o*-nitrobenzylidene)-γ-butyrolactone in the presence of an equivalent amount of hydrochloric acid.

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