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52. Zen-ichi Horii, Toyoshi Katagi, and Yasumitsu Tamura : Synthetic Studies on Sorigenins. V.[1] Synthesis of γ-Lactone of 3-Hydroxymethyl-4,5,7-trimethoxy-2-naphthoic Acid.*[1]

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As part of studies on the synthesis of the proposed structure,[2] 3-hydroxymethyl-1,6,8-trimethoxy-2-naphthoic acid γ-lactone (I), for α-sorigenin dimethyl ether, the synthesis of 3-hydroxymethyl-4,5,7-trimethoxy-2-naphthoic acid γ-lactone (II), an isomeric lactone of α-sorigenin dimethyl ether, was attempted. 4-Oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid (VII) appeared to be a very attractive intermediate for II as well as for I. This work was undertaken to investigate the preparation of VII and also of II started with VII.

Yagi[3] prepared VII from 3,5-dimethoxybenzoic acid by the following sequence of reactions. The Rosenmund reduction of 3,5-dimethoxybenzoyl chloride afforded the corresponding aldehyde, which was condensed with diethyl malonate and then, catalytically reduced to diethyl 3,5-dimethoxybenzylmalonate. Condensation of the malonate with ethyl bromoacetate followed by hydrolysis and decarboxylation yielded 2-(3,5-dimethoxybenzyl)succinic acid (V), which was cyclized, through the anhydride, employing anhyd. aluminum chloride in nitrobenzene to VII. Instead, we prepared V by condensation of 3,5-dimethoxybenzyl chloride[4] with diethyl 2-acetylsuccinate in the presence of sodium ethoxide and successive hydrolysis of the resulting diethyl 2-(3,5-dimethoxybenzyl)succinate (IV) with a sodium hydroxide solution. Over-all yield from 3,5-dimethoxybenzoic acid to V by our procedures was 34%, while 24% as result of our repetition by the method of Yagi. The yield of the cyclization of the anhydride VI to VII with anhyd. aluminum chloride according to the method of Yagi was 66%, while employment of polyphosphoric acid as a condensing reagent realized a little increase in yield (74%).

To obtain the key intermediates, (XII, XIII, and XIV) for preparing II, it was initially planned to treat the acid VII with formalin in the presence of sodium hydroxide[5] at room temperature or, to treat ethyl 4-hydroxy-5,7-dimethoxy-2-naphthoate (X) with formalin in the presence of hydrochloric acid[6] or with chloral hydrate in 90% sulfuric acid[7] according to the same methods as those reported in the cited literatures. However, it was found that, in the former reaction of VII, employment of one molar equivalent of formalin resulted in recovery of the starting material VII, while employment of a large excess of formalin resulted in formation of IX[8]. And the latter two reactions of X produced only resinous material. Concerning the preparation of X used in the above reactions, Yagi[9] obtained it by aromatization of VIII by fusing over palladium charcoal, since bromination of VIII to the monobromide did not proceed expectedly.

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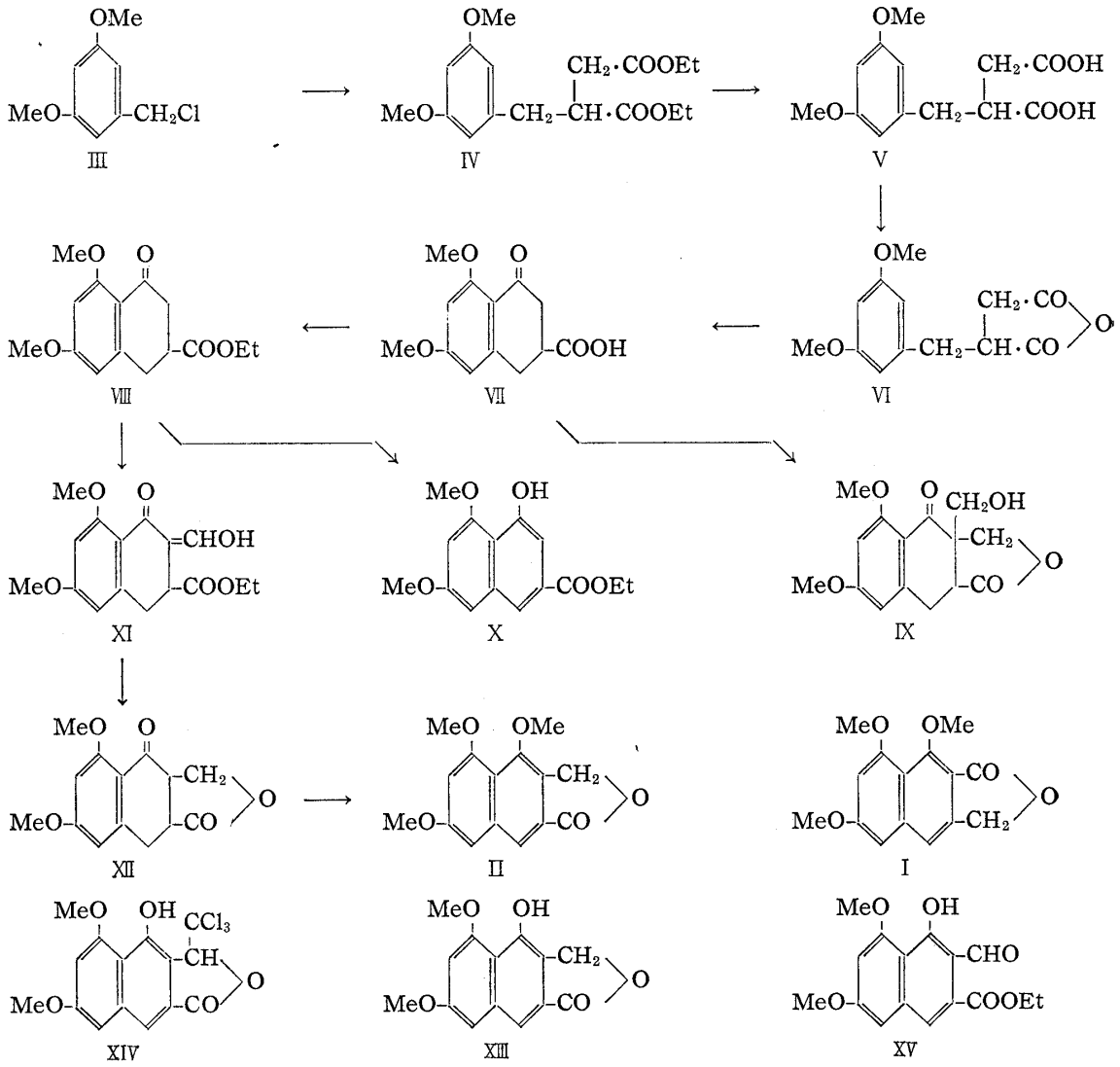
*1 Partly reported in Chem. & Ind. (London), **1960**, 1088 as communication.
*2 Toneyama, Toyonaka-shi, Osaka-fu (堀井善一, 加多木豊之, 田村恭光).
1) Part IV : This Bulletin, **11**, 305 (1963).
2) R. G. Haber, Z. Nikuni, H. Schmid, K. Yagi : Helv. Chim. Acta, **39**, 1654 (1956).
3) K. Yagi : J. Agric. Chem. Soc. Japan, **29**, 198 (1955).
4) R. Adams, S. Mekenzie, Jr., S. Loewe : J. Am. Chem. Soc., **70**, 666 (1948).
5) N. L. Drake, W. B. Tuemmber : *Ibid.*, **77**, 1204 (1955).
6) K. Yagi : J. Agric. Chem. Soc. Japan, **24**, 313 (1951).
7) Part III : This Bulletin, **10**, 898 (1962).
8) K. N. Campbell *et al.* : J. Am. Chem. Soc., **75**, 4681 (1953).
9) K. Yagi : J. Agric. Chem. Soc. Japan, **29**, 671 (1955).

We found that gradual addition of a high dilution of bromine in carbon disulfide gave considerably pure ethyl 3-bromo-4-oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate, which was dehydrobrominated with lithium chloride in dimethylformamide to X.

Condensation of VIII with ethyl formate in anhyd. benzene in the presence of sodium ethoxide afforded ethyl 3-hydroxymethylene-4-oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (XI). Although an attempt[1] to get XV from XI by bromination followed by dehydrobromination resulted in formation of only X, catalytic reduction of XI employing palladium charcoal gave 36% yield of XII. Bromination of XII, dehydrobromination of the resulting bromide and successive methylation with diazomethane in a mixture of ether and ethyl acetate gave 3-hydroxymethyl-4,5,7-trimethoxy-2-naphthoic acid γ-lactone (II), m.p. 205°, $\nu_{C=O}$ 1757 cm^{-1} (in chloroform).



Experimental

Diethyl 2-(3,5-Dimethoxybenzyl)succinate (IV)——To a stirred solution of diethyl 2-acetylsuccinate Na salt (prepared from 50 g. of diethyl 2-acetylsuccinate, 3.5 g. of Na powder and 200 cc. of anhyd. toluene) were added a solution of 2.7 g. of 3,5-dimethoxybenzyl chloride[4] in 60 cc. of anhyd. toluene, and 10 g. of NaI. The mixture was refluxed for 20 hr. After cooling, the reaction mixture was acidified with 10% HCl. The toluene layer was separated and the aqueous layer was extracted with benzene. The combined organic layer was washed with saturated $NaHCO_3$ solution and then H_2O, and

dried over $MgSO_4$. The solvent was removed, and the residue distilled under reduced pressure, giving 32 g. of a colorless oil, b.$p_{0.08}$ 182～190°. Redistillation gave 30 g. (64 %) of IV as a colorless oil, b.$p_{0.08}$ 182°. *Anal.* Calcd. for $O_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.02; H, 7.19. IR: $\nu_{max}^{CHCl_3}$ 1724 cm^{-1} (CO_2Et).

2-(3,5-Dimethoxybenzyl)succinic Acid (V)——A mixture of 30 g. of IV, 20 g. of NaOH and 100 cc. of H_2O was heated under reflux for 10 hr. After cooling, the reaction mixture was washed with Et_2O, acidified with dil. H_2SO_4 and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried and evaporated. The oily residue crystallized on treatment with benzene to give 24 g. (97 %) of V, m.p. 128° (lit.,[3] m.p. 128).

4-Oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (VII)——A mixture of 1.9 g. of V and 4 cc. of Ac_2O was refluxed for 20 min. and the solvent was removed under reduced pressure. To the residue VI was added 20 g. of polyphosphoric acid and the mixture was heated under stirring on a boiling water bath for 2 hr. After cooling, the mixture was poured into ice-water (100 cc.). The precipitate was collected, washed with H_2O, and recrystallized from dil. EtOH to give 1.3 g. (73.5 %) of VII, m.p. 199° (lit.,[3] m.p. 198°).

Ethyl 4-Oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (VIII)——A solution of 1.8 g. of VII, 17 cc. of abs. EtOH, 32 cc. of anhyd. benzene and 3 drops of conc. H_2SO_4 was heated under reflux (through Dean-Stark water-separator) for 10 hr. The solvent was removed, the residue was extracted with AcOEt, the AcOEt extract was washed with $NaHCO_3$ solution and H_2O, and dried over $MgSO_4$. Removing the solvent left an oily residue, which crystallized on treatment with Et_2O, giving 1.6 g. of colorless needles VIII, m.p. 92～93° (lit.,[3] m.p. 85～87.5°). *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.65; H, 6.36.

Ethyl 4-Hydroxy-5,7-dimethoxy-2-naphthoate (X)——To a stirred solution of 1.0 g. of VIII in 70 cc. of CS_2 was added dropwise a solution of 580 mg. of Br_2 in 20 cc. of CS_2 at room temperature over a period of 4 hr., and stirring was continued for an additional hour. The reaction mixture was washed with H_2O, $NaHCO_3$ solution and then H_2O, and dried over $MgSO_4$. Evaporation of the solvent gave the crude bromide as an oil. The crude bromide was heated with 0.23 g. of LiCl in 10 cc. of dimethylformamide on a boiling water bath for 4 hr. When cool, the reaction mixture was diluted with Et_2O, washed with H_2O and dried over $MgSO_4$. The solvent was removed and the residue was purified by chromatography using alumina and benzene as an eluent. The material eluted with benzene was recrystallized from EtOH to give 0.65 g. of X as colorless needles, m.p. 141～143°. An analytical sample was prepared by recrystallization from EtOH, m.p. 144.5° (lit.,[9] m.p. 133～135°). *Anal.* Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.81. Found: C, 65.51; H, 6.07.

4-Oxo-3,3-bis(hydroxymethyl)-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid γ-Lactone (IX)——A mixture of 510 mg. of VI, 1 cc. of 37% HCHO and 5 cc. of 10% KOH was stirred at room temperature for 95 hr. The solution was acidified with dil. HCl and extracted with AcOEt. The AcOEt extract was washed with $NaHCO_3$ solution and H_2O, and dried over $MgSO_4$. Removal of the solvent left 227 mg. of a light yellow oil, which crystallized on treatment with EtOH. Recrystallization from EtOH gave 154 mg. of IX as colorless prisms, m.p. 164～166°. An analytical sample was prepared by several recrystallizations from EtOH, m.p. 168°. *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.37; H, 5.35. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1770 (lactone), 1648 (CO). When this reaction was carried out using a theoretical amount of HCHO and reaction time of 15 hr., most of the starting material was recovered.

Ethyl 3-Hydroxymethylene-4-oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (XI)——To a suspension of 0.3 g. of NaH in 20 cc. of anhyd. benzene was added 1 cc. of abs. EtOH and the mixture was stirred at room temperature for 3 hr. To this solution was added dropwise 2 g. of HCO_2Et, followed by a solution of 1 g. of VIII in 40 cc. of anhyd. benzene over a period of 30 min. After the addition was completed, stirring was continued for 4.5 hr. The reaction mixture was poured into 100 cc. of ice water. The separated aqueous layer was washed with benzene and poured into ca. 200 cc. of ice water containing 2 cc. of conc. H_2SO_4. The resulting precipitate was extracted with benzene. The benzene solution was washed with H_2O, dried over $MgSO_4$ and evaporated. The residue (850 mg.) was recrystallized from 1 cc. of EtOH to give 670 mg. (61 %) of a colorless material, m.p. 101°. The melting point of this compound was raised up to 103° by several recrystallizations from the same solvent. *Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.81; H, 5.91.

3-Hydroxymethyl-4-oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid γ-Lactone (XII)——A solution of 500 mg. of XI in 100 cc. of EtOH was catalytically reduced using 230 mg. of 10% Pd-C as a catalyst at room temperature and atmospheric pressure. It took 6 hr. to absorb a theoretical amount of H_2. The catalyst was removed by filteration and washed with EtOH. The filtrate and washing were combined and evaporated. The residue was recrystallized from 0.5 cc. of EtOH, giving 154 mg. of XII as colorless prisms, m.p. 197°. An analytical sample melted at 198°. *Anal.* Calcd. for $C_{14}H_{15}O_5$: C, 64.11; H, 5.38. Found: C, 64.43; H, 5.44. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (lactone), 1658 (CO).

3-Hydroxymethyl-4,5,7-trimethoxy-2-naphthoic Acid γ-Lactone (II)——To a stirred solution of 100 mg. of XII in 30 cc. of $CHCl_3$ was added dropwise a solution of 62 mg. of Br_2 in 30 cc. of $CHCl_3$ at room temperature over a period of 3 hr., and stirring was continued for 1 hr. after the addition was completed. The reaction mixture was washed with $NaHCO_3$ solution and H_2O, and dried over $MgSO_4$. The solvent was removed, and the residue was heated with 100 mg. of LiCl and 5 cc. of dimethylformamide on a boiling water bath for 1 hr. After cooling, 50 cc. of H_2O was added and the whole mixture was extracted with AcOEt. The AcOEt extract was washed with water and dried over $MgSO_4$. A solution of a large excess of CH_2N_2 in Et_2O was added to the AcOEt extract and allowed to stand at room temperature for 2 days. After addition of AcOH to destroy the excess of CH_2N_2, the solution was washed with $NaHCO_3$ solution and H_2O, dried over $MgSO_4$ and evaporated. Recrystallizations of the residue from 10 cc. of EtOH gave 67 mg. (64 %) of colorless needles, m.p. 201°. This compound was purified by chromatography using silica-gel and $CHCl_3$ as an eluent. An analytical sample melted at 205°. *Anal.* Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found : C, 65.52; H, 5.12. IR : $\nu_{max}^{CHCl_3}$ 1757 cm^{-1} (lactone).

Summary

4-Oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid (VII) is expected to serve as a key intermediate in the synthesis of the proposed structure for α-sorigenin dimethyl ether (3-hydroxymethyl-1,6,8-trimethoxy-2-naphthoic acid γ-lactone (I)). The reported method for VII was improved and the synthesis of 3-hydroxymethyl-4,5,7-trimethoxy-2-naphthoic acid γ-lactone (II) started with VII was carried out. The reaction scheme is shown in chart.

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53. Zen-ichi Horii, Toyoshi Katagi, and Yasumitsu Tamura : Synthetic Studies on Sorigenins. VI.[1] Synthesis of γ-Lactone of 3-Hydroxymethyl-1,6,8-trimethoxy-2-naphthoic Acid (α-Sorigenin Dimethyl Ether). (1).*1

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Nikuni, Schmid *et al.*, in 1956, showed that α- and β-sorigenin, aglycons of α- and β-sorinin isolated[2] from the bark of *Rhamnus japonica* MAXIM., should have the structural formulas,[3,4] 3-hydroxymethyl-6-methoxy-1,8-dihydroxy-2-naphthoic acid γ-lactone (I : R=H, R′=CH_3O) and 3-hydroxymethyl-1,8-dihydroxy-2-naphthoic acid γ-lactone (I : R=R′=H), respectively. Recently, Horii, *et al.* synthesized[5] β-sorigenin dimethyl ether (I : R=CH_3, R′=H) and established the structure of β-sorigenin. In this paper, 3-hydroxymethyl-1, 6, 8-trimethoxy-2-naphthoic acid γ-lactone (I : R=CH_3, R′=CH_3O) was synthesized by partial reduction[5,6] with lithium alminum hydride of the half ester (VIII)

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1) Part V : This Bulletin, **11**, 309 (1963).
2) Z. Nikuni : J. Agric. Chem. Soc. Japan, **14**, 352 (1938).
3) R. G. Haber, Z. Nikuni, K. H. Schmid, Yagi : Helv. chim. Acta, **39**, 1654 (1956).
4) Z. Nikuni : J. Agric. Chem. Soc. Japan, **18**, 496 (1942); **17**, 779 (1941); **15**, 109, 283, 1179 (1939).
5) Part II : This Bulletin, **10**, 893 (1962).
6) Part I : *Ibid.*, **10**, 887 (1962).