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140. Zen-ichi Horii, Yasumitsu Tamura, and Teiji Tanaka : Synthetic Studies on Sorigenins. II.[1] Synthesis of β-Sorigenin Dimethyl Ether.[2]

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The structural formulae of α- and β-sorigenin were first proposed as (I : R=CH_3O, R′=H) and (I : R, R′=H), respectively.[3] Recently, Haber, Nikuni, Schmid, and Yagi[4] reexamined their chemical and physical properties, and revised the structures to (II : R=CH_3O, R′=H) and (II : R, R′=H). The following observations were pointed out as the major reasons for the revision of their structural formulae. Compound (I : R=H, R′=CH_3) synthesized did not coincide with the natural β-sorigenin dimethyl ether, while both (I : R=H, R′=CH_3) and β-sorigenin dimethyl ether were led to 1,8-dimethoxy-2,3-naphthalenedimethanol by reduction with lithium aluminium hydride. The strong absorption at 1730~1725 cm^{-1} ($\nu_{C=O}$) in the infrared spectra of sorigenins should have been ascribed to an intramolecular hydrogen-bonding in the compound (II : R′=H). These structures would have been further supported from view of the biogenesis. This paper describes the synthesis of β-sorigenin dimethyl ether which was carried out according to the methods reported in the preceding paper.[1] The result provides the synthetic confirmation for the structural formulae (II : R, R′=H) of β-sorigenin.

As the starting material in this work, 7-methoxy-1-indanone (III) was prepared by the method described in the literature.[5] Compound (III) was condensed with diethyl carbonate in the presence of sodium hydride to give 2-ethoxycarbonyl-7-methoxy-1-indanone (IV) (70%), which was converted to ethyl 1-oxo-2-ethoxycarbonyl-7-methoxy-2-indanacetate (V) (74%) by the action of ethyl bromoacetate. Boiling with an ethanolic potassium hydroxide transformed (V) to (2-carboxy-3-methoxybenzyl)succinic acid (VI) in 76% yield. The trimethyl ester (VII), prepared by treatment of (VI) with diazomethane, was subjected to the Dieckmann reaction under various conditions. This Dieckmann reaction was found to be accomplished with sodium in boiling toluene, but the yield of dimethyl 1-oxo-8-methoxy-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate (VIII) was 33% at the best. Bromination of (VIII) with bromine followed by heating with 2,4,6-collidine gave dimethyl 1-hydroxy-8-methoxy-2,3-naphthalenedicarboxylate (X) (52% overall yield), which was methylated with methyl iodide and potassium carbonate in acetone to dimethyl 1,8-dimethoxy-2,3-naphthalenedicarboxylate (XI) in 86% yield. Compound (XI) was hydrolyzed with an ethanolic potassium hydroxide and the resulting 1,8-dimethoxy-2,3-naphthalenedicarboxylic acid (XII) was converted to the corresponding anhydride (XIII) with acetyl chloride in 63% overall yield. When (XIII) was reduced with zinc and conc. hydrochloric acid in a mixture of glacial acetic acid and dioxane the only material isolated was a lactone of m.p. 176°, which was shown to be identical with natural β-sorigenin dimethyl ether by mixed melting point and comparison of their infrared and ultraviolet spectra. The structure of the lactone of m.p. 176° or β-sorigenin dimethyl ether could be assigned as 3-hydroxymetyl-1,8-dimethoxy-2-naphtoic acid γ-lactone (XIV) from the following facts. Of two isomeric lactones of 3-hydroxymethyl-

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1) Part I : This Bulletin, **10**, 887 (1962).

2) Partly reported in Chem. & Ind. (London), **1959**, 1576 as communication.

3) Z. Nikuni : J. Agr. Chem. Soc. Japan, **18**, 496 (1942); Z. Nikuni, H. Hitsumoto : *Ibid.*, **20**, 283 (1944).

4) R.G. Haber, Z. Nikuni, H. Schmid, K. Yagi : Helv. chim. Acta, **39**, 1654 (1956).

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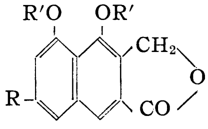
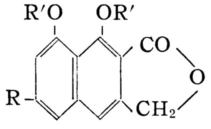
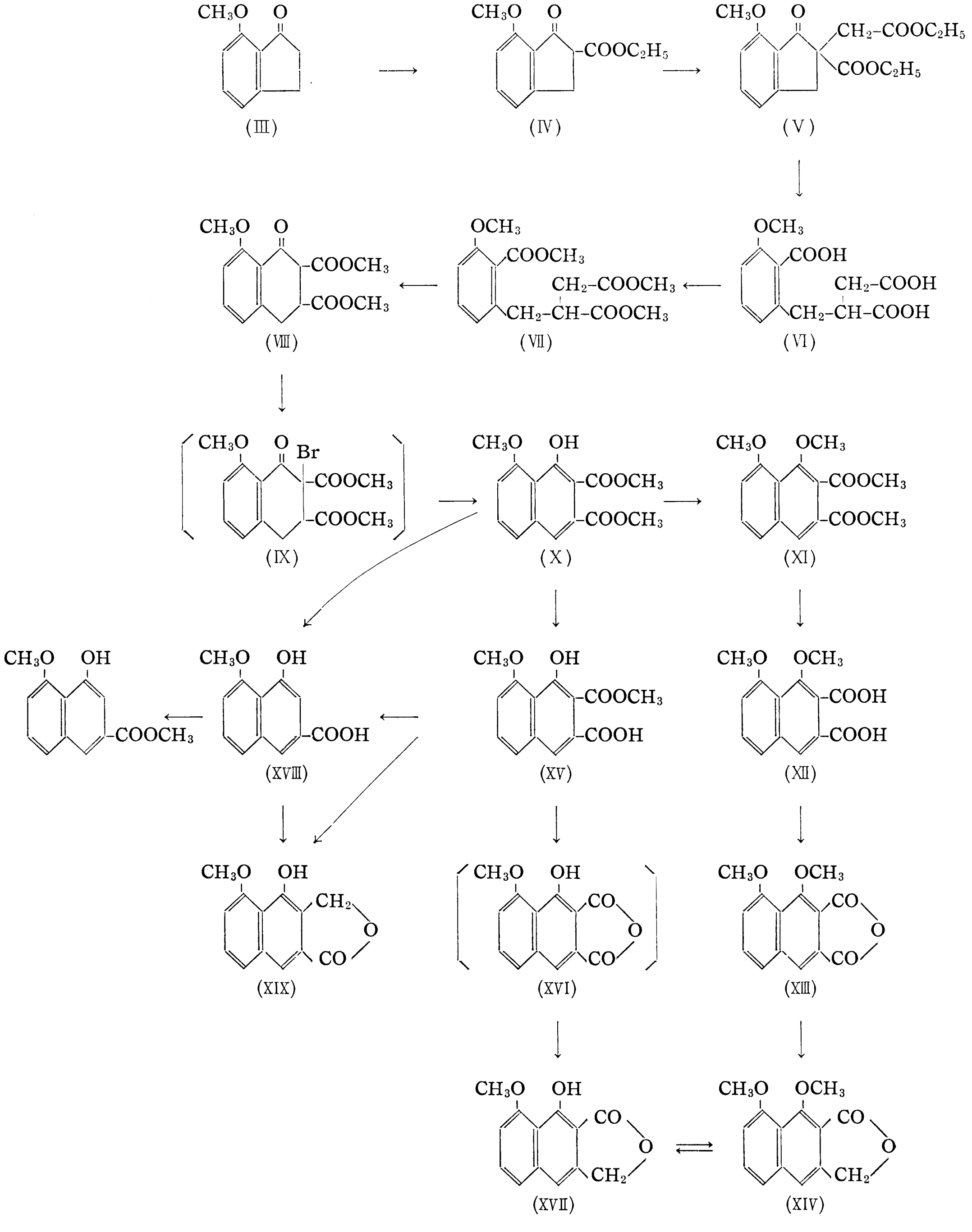


(I)



(II)



4-hydroxy-5-methoxy-2-naphthoic acid γ-lactone (XIX) and 1-hydroxy-3-hydroxymethyl-8-methoxy-2-naphthoic acid γ-lactone (XVII) prepared as described below, compound (XIX) was found to be identical with an authentic sample of 3-hydroxymethyl-4-hydroxy-5-methoxy-2-naphthoic acid γ-lactone offered by H. Schmid and the other, whose structure would be settled as 1-hydroxy-3-hydroxymethyl-8-methoxy-2-naphthoic acid γ-lactone which was transformed to (XIV) with diazomethane.

Compound (X) was hydrolyzed to the halfester (XV) by boiling with an anhydrous methanolic potassium hydroxide in 86% yield. When this hydrolysis was carried out using a methanolic potassium hydroxide containing a few drops of water, the product was eleutherolic acid (XVIII). Reduction of the halfester (XV) with lithium aluminium hydride in a mixture of ether and tetrahydrofuran gave (XIX), whose structure was confirmed by direct comparison of melting points and infrared spectra with a sample of (XIX) prepared by Schmid, *et al.* When the sublimation product of (XV), which is assumed by infrared analysis to be a mixture of the halfester and corresponding anhydride (XVI), was reduced with zinc and conc. hydrochloric acid in a mixture of glacial acetic acid and dioxane, the only product isolated was (XVII).

β-Sorigenin dimethyl ether gave (XVII) by boiling with conc. hydrochloric acid in glacial acetic acid. However, attempts to obtain β-sorigenin by demethylation of its dimethyl ether (XIV) using aluminium chloride, 48% HBr and conc. hydrochloric acid failed.

Experimental

Ethyl 1-Oxo-2-ethoxycarbonyl-7-methoxy-2-indanacetate (V)——A mixture of 7 g. of diethyl carbonate, 15 cc. of anhyd. benzene and 1.5 g. of NaH was heated at 65°(bath temperature) with stirring and then a solution of 5 g. of 7-methoxy-1-indanone (III) in anhyd. benzene was added dropwise during the course of 3.5 hr. Stirring was continued at the same temperature for an additional 1.5 hr. and the reaction mixture was allowed to stand overnight at room temperature. The solid product was washed with benzene and decomposed with 10% HCl. The separated oily material was extracted with benzene. The benzene extract was washed with water, dried over Na_2SO_4 and the solvent was removed. Distillation of the residue under reduced pressure gave 5 g. (70%) of crude ethyl 1-oxo-7-methoxy-2-indancarboxylate (IV), b.$p_{0.2}$ 165°. This material gave a purple color with alcoholic $FeCl_3$ solution.

A solution of 2 g. of (IV) in 16 cc. of anhyd. benzene was added to a suspension of EtONa in anhyd. benzene (prepared from 0.2 g. of powdered Na, 14 cc. of anhyd. benzene and 0.4 g. of EtOH) and refluxed for 2 hr. Then a solution of 2.2 g. of ethyl bromoacetate in 2 cc. of anhyd. benzene was added and the reaction mixture was stirred under reflux for 7 hr. Precipitated NaBr was removed by filtration and the filtrate was washed with saturated $NaHCO_3$ solution and water. After drying over Na_2SO_4, the solvent was removed and the residue was distilled under reduced pressure, giving 2 g. (74%) of yellow viscous oil, b.$p_{0.1}$ 185°. *Anal.* Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found : C, 63.80; H, 6.28.

(2-Carboxy-3-methoxybenzyl)succinic Acid (VI)——A mixture of (V), 2 g. of KOH, 1.2 cc. of water and 4 cc. of EtOH was heated under reflux for 2 hr. After evaporation of EtOH from the reaction mixture under reduced pressure, the residue was poured ice-HCl and extracted with AcOEt. The extract was shaken with saturated $NaHCO_3$ solution, the alkaline layer was acidified with ice-HCl and re-extracted with AcOEt. The AcOEt extract was washed, dried and evaporated. The residue solidified on trituration. Recrystallization from EtOH-benzene gave 1.3 g. (76%) of needles, m.p. 167.5°. *Anal.* Calcd. for $C_{13}H_{14}O_7$: C, 55.32; H, 5.00. Found : C, 55.22; H, 4.97. IR ν_{max}^{Nujol} cm^{-1} : 2630, 1700.

Dimethyl(2-Methoxycarbonyl-3-methoxybenzyl) succinate (VII)——Excess of CH_2N_2 was passed through an ice-cooled suspension of 5 g. of (VI) in Et_2O until solid of (VI) dissolved. After standing for 3 days in an ice-box, glacial AcOH was added to destroy excess of CH_2N_2. The whole solution was washed with saturated $NaHCO_3$ solution and water and dried over Na_2SO_4. The solvent was removed and the residue was distilled under reduced pressure, giving 5.2 g. (91%) of light yellow viscous oil, b.$p_{0.15}$ 168°. *Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found : C, 58.94; H, 6.10. IR : ν_{max}^{Nujol} 1738 cm^{-1}.

Dimethyl 1-Oxo-8-methoxy-1,2,3,4-tetrahydro-2,3-naphthalenedicarboxylate (VIII)——To a suspension of 0.1 g. of powdered Na in 5 cc. of anhyd. toluene was added a toluene solution of 1.7 g. of (VII) and the reaction mixture was stirred under reflux for 10 hr. on a boiling water bath. The reaction mixture was cooled and poured into ice-HCl. The toluene layer was separated and the aqueous layer was extracted with benzene. The combined organic layer was extracted with 1% NaOH. The alkaline extract was acidified with ice-HCl and re-extracted with AcOEt. The AcOEt extract was washed with saturated $NaHCO_3$ solution and water successively, and dried over Na_2SO_4. The solvent was removed, and the residue solidified on trituration. Recrystallization from EtOH gave colorless crystals of m.p. 121.5°. The yield of (VIII) was 400 mg. (26%). This material gave a purple color with absolute ethanolic $FeCl_3$ solution. *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found : C, 61.54; H, 5.48. IR ν_{max}^{Nujol} cm^{-1} : 1756, 1738, 1677. $\nu_{max}^{CHCl_3}$ cm^{-1} : 1750, 1675.

Dimethyl 1-Hydroxy-8-methoxy-2,3-naphthalenedicarboxylate (X)——To a solution of 250 mg. of (VIII) in 5 cc. of $CHCl_3$ was added dropwise a solution of 150 mg. of Br_2 in 5 cc. of $CHCl_3$ and stirring was continued at room temperature for 1.5 hr. The reaction mixture was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 290 mg. of crude (IX) as yellow oil. The crude (IX) was heated with 3 g. of 2,4,6-collidine on a boiling water bath for 2 hr. After cooling, Et_2O was added to complete the precipitation of 2,4,6-collidine hydrobromide, which was filtered off. The filtrate was washed with water, dil. HCl and water successively and dried over Na_2SO_4. Removal of the solvent left 170 mg. of crystals, which were recrystallized from EtOH to give 130 mg. (57%) of colorless pillars, m.p. 145.5°. *Anal.* Calcd. for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86. Found : C, 61.79; H, 4.74. IR ν_{max}^{Nujol} cm^{-1} : 3333, 1724, 1706.

Dimethyl 1,8-Dimethoxy-2,3-naphthalenedicarboxylate (XI)——A mixture of 1.4 g. of (X), 7.3 g. of MeI, 3.3 g. of anhyd. K_2CO_3 and 50 cc. of anhyd. Me_2CO was refluxed for 50 hr. A 0.5 cc. portion of MeI was added every 9 hr. during this period. After evaporation of Me_2CO, the residue was dissolved in water and extracted with benzene. The benzene extract was washed with 5% NaOH and then water, dried over Na_2SO_4 and the solvent was evaporated. The residue solidified on trituration. Recrystallization from MeOH gave 1.16 g. (86%) of colorless needles, m.p. 112°. *Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found : C, 62.86; H, 5.07. IR : ν_{max}^{Nujol} cm^{-1}:1724.

1,8-Dimethoxy-2,3-naphthalenedicarboxylic Acid (XII)——A solution of 1.16 g. of (XI), 840 mg. of KOH, 100 cc. of MeOH and 10 drops of water was heated under reflux for 13 hr. After evaporation of MeOH, the residue was dissolved in water and washed with benzene. The aqueous layer was acidified with dil. HCl and extracted with AcOEt. The AcOEt extract was shaken with saturated $NaHCO_3$ solution, the alkaline extract was again acidified with dil. HCl and re-extracted with AcOEt. The AcOEt extract was washed, dried and the solvent was removed. The resulting light brown crystals recrystallized from dil. MeOH gave 0.95 g. (90%) of pale yellow needles, m.p. 250° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found : C, 61.09; H, 4.68. IR ν_{max}^{Nujol} cm^{-1} : 1724 (m), 1681 (s).

1,8-Dimethoxy-2,3-naphthalenedicarboxylic Anhydride (XIII)——A suspension of 950 mg. of (XII) in AcCl was heated under reflux for 3 hr. Removal of AcCl by distillation left yellow crystals, which were recrystallized from AcOEt to give 600 mg. (70%) of yellow needles, m.p. 250°. *Anal.* Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found : C, 64.65; H, 4.19. IR ν_{max}^{Nujol} cm^{-1} : 1825, 1770.

Hydrolysis of (X) to form 3-Methoxycarbonyl-4-hydroxy-5-methoxy-2-naphthoic Acid (XV)—— A solution of 400 mg. of (X), 300 mg. of KOH and 15 cc. of MeOH was heated under reflux for 8 hr. After evaporation of MeOH, the residue was dissolved in water and acidified with dil. HCl. The deposited solid material was washed with water and recrystallized from toluene to give 328 mg. (86%) of pale yellow crystals, m.p. 290° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found : C, 60.80; H, 4.30. IR ν_{max}^{Nujol} cm^{-1} : 3289, 2591 (broad), 1724, 1681.

When the above hydrolysis was carried out using 90% MeOH in the place of MeOH, the product was 4-hydroxy-5-methoxy-2-naphthoic acid (eleutherolic acid) (XVIII), m.p. 246.5°. It was also found that recrystallization of (XV) from dil. MeOH gave (XVIII). *Anal.* Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found : C, 66.43; H, 4.69. IR ν_{max}^{Nujol} cm^{-1} : 3333, 2500 (broad), 1681~1667 (broad).

Methyl 4-Hydroxy-5-methoxy-2-naphthoate——A suspension of 100 mg. of (XVIII) in 10 cc. of anhyd. MeOH was saturated with dry HCl gas and the reaction mixture was slightly warmed to make it a clear solution. After standing overnight, the reaction mixture was poured into crushed ice and the precipitated crystals were washed with water and then $NaHCO_3$ solution. The alkaline-insoluble crystals were washed with water and recrystallized from MeOH to give 85 mg. of colorless needles, m.p. 131°. *Anal.* Calcd. for $C_{13}H_{12}O_4$: C, 67.20; H, 5.21. Found : C, 67.25; H, 5.31. IR ν_{max}^{Nujol} cm^{-1}: 3333, 1717.

1-Hydroxy-3-hydroxymethyl-8-methoxy-2-naphthoic Acid γ-Lactone (XVII) i) From (XV)——Sublimation of (XV) at 190~195° and 0.02 mm.Hg gave yellow solid of m.p. 308°. This material was supposed to be a mixture of the starting material (XV) and the anhyd. (XVI) of 1-hydroxy-8-methoxy-2,3-naphthalenedicarboxylic acid and used without further purification. The sublimation product (100 mg.) was suspended in a mixture of 2 cc. of dioxane, 660 mg. of AcOH and 660 mg. of conc. HCl and to the suspension was added 300 mg. of Zn dust with occasional shaking over 15~30 min. period.

The reacton mixture was heated for 11 hr. on a boiling water bath, and then concentrated to dryness. The residue was extracted with AcOEt. The extract was washed with water, saturated $NaHCO_3$ solution and water and dried. Removing of the solvent left 20 mg. of a residue, which was crystallized from EtOH to give colorless needles of m.p. 235°. *Anal.* Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found : C, 67.17; H, 4.45. IR ν_{max}^{Nujol} cm^{-1} : 3300, 1745.

Acidification of the $NaHCO_3$ washing described above gave 50 mg. of eleutherolic acid, m.p. 245°, which was not depressed on admixture with a sample of (XVIII) obtained by the hydrolysis of the diester (X) as described above.

ii) From β-Sorigenin Dimethyl Ether (XIV)——A suspension of 50 mg. of β-sorigenin dimethyl ether, 30 cc. of AcOH and 15 cc. of conc. HCl was heated on a boiling water bath for 1 hr. under a nitrogen atmosphere and concentrated to dryness under reduced pressure. The green-yellow residue was purified by chromatography through a silica gel column using $CHCl_3$ as eluent. Recrystallization from EtOH gave colorless needles of m.p. 235°. IR ν_{max}^{Nujol} cm^{-1} : 3300, 1745.

This compound was shown to be identical with a sample of (XVII) prepared above in i) by mixed melting point and comparison of their IR spectra.

3-Hydroxymethyl-1,8-dimethoxy-2-naphthoic Acid γ-Lactone (β-Sorigenin Dimethyl Ether) (XIV)
i) From (XIII)——To a solution of 100 mg. of (XIII), 1 cc. of dioxane, 330 mg. of AcOH and 330 mg. of conc. HCl was added 150 mg. of Zn dust with occasional shaking over 15~30 min. period and the mixture was heated for 11 hr. on a boiling water bath. The reaction mixture was concentrated to dryness and the residue was extracted with AcOEt. The AcOEt solution was washed with water, saturated $NaHCO_3$ solution and water dried and the solvent was removed. The residue was chromatographed on alumina. Elution with benzene-petr. benzin (10:2) gave two fractions : (1) slightly yellow prisms, m.p. 151°, on recrystallization from EtOH. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found : C, 68.67; H, 4.95. IR : ν_{max}^{Nujol} 1754 cm^{-1}, $\nu_{max}^{CHCl_3}$ 1767 cm^{-1}. UV λ_{max}^{EtOH} mμ (log ε) : 284 (4.75), 304 (3.57), 316 (3.60), 355 (3.80). This material seems probably to be a mixture of (XIV) and the methyl ether of (XIX) but has not been characterized. (2) Slightly yellow prisms, m.p. 176°, on recrystallization from benzene or EtOH. This material was shown to be identical with natural β-sorigenin dimethyl ether (m.p. 176°) by mixed melting point and comparison of their IR and UV spectra. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H,4.95. Found : C, 68.75; H, 4.83. IR : ν_{max}^{Nujol} 1754 cm^{-1}, $\nu_{max}^{CHCl_3}$ 1767 cm^{-1}. UV λ_{max}^{EtOH} mμ (log ε) : 248 (4.75), 304 (3.56), 316 (3.58) 355 (3.78).

ii) From (XVII)——Excess of CH_2N_2 was passed through an ice-cooled suspension of 18 mg. of (XVII) in Et_2O and the reaction mixture was allowed to stand for 3 days in an ice-box. After addition of glacial AcOH to decompose excess of CH_2N_2, the reaction mixture was washed successively with water, saturated $NaHCO_3$ solution and water, and dried over Na_2SO_4. The solvent was removed and the residue (18 mg.) was purified by alumina chromatography using benzene as eluent. The eluted crystals were recrystallized from benzene to give colorless pillars or scales of m.p. 176°. IR : $\nu_{max}^{CHCl_3}$ 1767 cm^{-1}.

This compound was shown to be identical with natural β-sorigenin dimethyl ether by mixed melting point and comparison of IR spectra.

3-Hydroxymethyl-4-hydroxy-5-methoxy-2-naphthoic Acid γ-Lactone (XIX)——To a solution of 15 mg. of the halfester (XV) in 5 cc. of anhyd. tetrahydrofuran was added a solution of 35 mg. of $LiAlH_4$ in 10 cc. of anhyd. Et_2O at 0° under vigorous stirring. After the addition was completed, the mixture was stirred at the same temperature for 6 hr. AcOEt was added to destroy excess of $LiAlH_4$ and the solvent was removed. The residue was poured into dil. HCl and extrated with AcOEt. The AcOEt extract was washed with water, saturated $NaHCO_3$ solution and then water, and dried over Na_2SO_4. Evaporation of the solvent and chromatography of the residue through silica gel using $CHCl_3$ as eluent gave 1 mg. of colorless needles of m.p. 248° (decomp.) (from EtOH). IR ν_{max}^{Nujol} cm^{-1} : 3333, 1754. The melting point of this compound was undepressed on admixture with an authentic sample of (XIX), which was prepared by Nikuni, Schmid, *et al.*

From the $NaHCO_3$ washing described above was recovered 14 mg. of the unchanged (XV) after acidification with HCl.

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Summary

Synthesis of β-sorigenin dimethyl ether (XIV) and 3-hydroxymethyl-4-hydroxy-5-methoxy-2-naphthoic acid γ-lactone (XIX) were described. The structure of β-sorigenin was synthetically established as 3-hydroxymethyl-1,8-dihydroxy-2-naphthoic acid γ-lactone (II : R, R′=H).

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