Summary

A sensitive spot test for active methylene compounds was established by adding sodium dihydrogen phosphate in the alkaline reaction mixture of either trinitrobenzene or picric acid. A blank color faded or diminished in this method, and the developed coloration increased wtih a few exceptions. The color and a limit of detection of many active methylene compounds were tabulated.

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51. Zen-ichi Horii, Toyoshi Katagi, Yasumitsu Tamura, Teiji Tanaka, and Yasuhiko Yamawaki : Synthetic Studies on Sorigenins. IV.[1] Synthesis of γ-Lactone of 3-Hydroxymethyl-4-methoxy-2-naphthoic Acid.

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In continuation of the previous work[1] on the preparation of 3-hydroxymethyl-4-methoxy-2-naphthoic acid γ-lactone (VI), two new routes leading to VI from ethyl 4-oxo-1,2,3,4-tetrahydro-2-naphthoate (I)[2] were established, which involved aromatization and successive reduction of the 3-hydroxymethylene and the 3-ethoxalyl derivatives of I, respectively, as shown in Charts 1 and 2.

Ethyl 3-hydroxymethylene-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (II), which was obtained by condensation[3] of I with ethyl formate in benzene in the presence of sodium ethoxide, was brominated with bromine in chloroform to ethyl 3-bromo-3-formyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (III). Dehydrobromination of III by heating with N,N-dimethylaniline in a water bath for 2 hours gave ethyl 3-formyl-4-hydroxy-

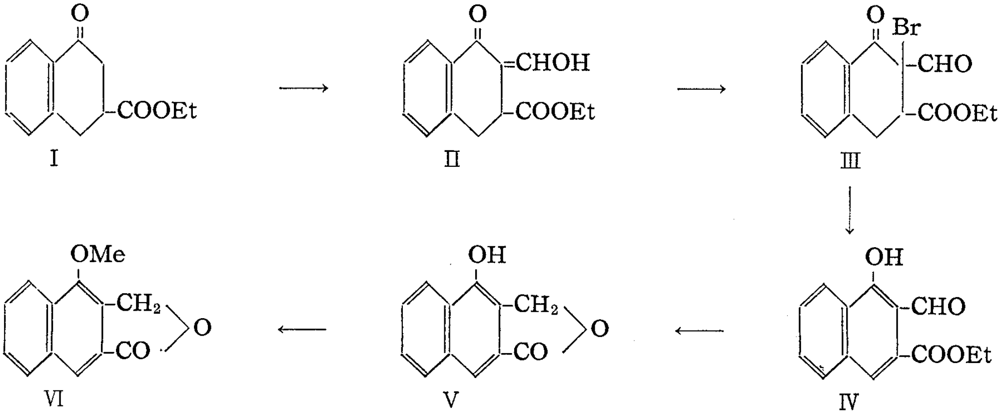


Chart 1.

[*1] Toneyama, Toyonaka-shi, Osaka-fu (堀井善一, 加多木豊之, 田村恭光, 田中悌二, 山脇泰彦).

1) Part III : This Bulletin, **10**, 898 (1962).

2) W.F. Beech, N. Legg : J. Chem. Soc., **1949**, 1887.

3) W.J. Gensler, C.M. Samour, S. Yi Wang, F. Johnson : J. Am. Chem. Soc., **82**, 1714 (1960).

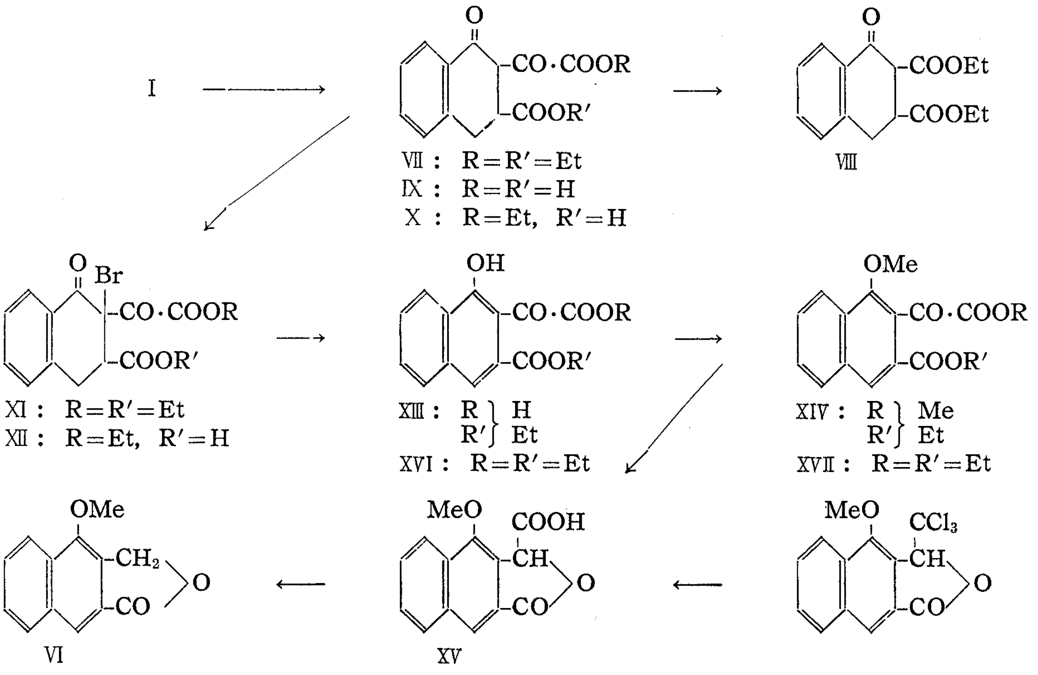
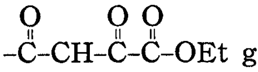
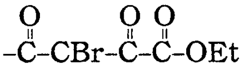


Chart 2.

2-naphthoate (IV), which was reduced with sodium borohydride followed by methylation with diazomethane to give VI.[1]

The other route consists of a similar series of reactions on the 3-ethoxalyl derivative of I. Condensation[4] of I with diethyl oxalate in ether in the presence of sodium hydride gave ethyl 3-ethoxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VII), which was easily decarbonylated[4] on heating over glass wool to diethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (VIII). When this condensation was carried out using sodium ethoxide in benzene, a product was found to be partially hydrolyzed 3-ethoxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (X). Bromination of VII and X with bromine in chloroform gave the corresponding bromides, XI and XII, respectively. The structural assignment of X and XII was based on their infrared spectra. Compnund X has two absorptions due to both of the ester and carboxylic acid groups at 1718 and 1706 cm^{-1}, and XII has at 1754 and 1721 cm^{-1}. Since compound (VII) shows only one ester absorption at 1718 cm^{-1} and compound XI does two ester absorptions at 1751 and 1724 cm^{-1}, it would be most reasonable to conclude that the absorptions at 1718 cm^{-1} in VII and X are ascribed to the ester group in the  $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{CH}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OEt}$ grouping, the absorptions[5] at 1751 and 1754 cm^{-1} in XI and XII to the ester group in the  $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{CBr}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OEt}$ grouping, and thus the absorptions at 1706 and 1721 cm^{-1} in X and XII to the carboxylic acid group, respectively. The bromide XI was dehydrobrominated with morpholine at room temperature followed by methylation with methyl iodide and potassium carbonate in acetone to give the diester XIV, which was reduced with sodium borohydride[6] in water to 3-(carboxyhydroxymethyl)-4-methoxy-2-naphthoic acid γ-lactone (XV). Compound XV was decarboxylated by the method reported in the previous paper[1] to give VI.

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[4] E. Buchta, H. Galster, F. Luther: Chem. Ber., **82**, 126 (1949); W. Hückel, E. Goth: *Ibid.*, **57**, 1285 (1924).

[5] L. J. Bellamy: "The Infra-red Spectra of Complex Molecules" p. 152 (1954); E. D. Stecher, A. Clements: J. Am. Chem. Soc., **76**, 503 (1954).

[6] E. B. Reid, J. R. Siegel: J. Chem. Soc., **1954**, 520.

Experimental

Ethyl 3-Hydroxymethylene-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (II)——To a suspension of EtONa in benzene (prepared from 1.4 g. of NaH, 3 cc. of abs. EtOH and 100 cc. of anhyd. benzene) was added 8.4 g. of ethyl formate, and the mixture was stirred at room temperature for 30 min. A solution of 4.2 g. of ethyl 4-oxo-1,2,3,4-tetrahydro-2-naphthoat (I)[2] in 50 cc. of anhyd. benzene was added dropwise to the above mixture during a period of 30 min., and was stirred for 3 hr. at room temperature before being poured into 150 cc. of ice water. The aqueous layer was separated, washed with benzene and poured into 150 cc. of ice water containing 4 cc. of conc. H_2SO_4. The precipitate was taken up in 200 cc. of Et_2O, the resulting Et_2O solution washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent left 4.3 g. of crude II, which was recrystallized from Et_2O-petr. ether giving 3.2 g. (68%) of colorless plates, m.p. 50°. An alcoholic $FeCl_3$ solution of this compound gave a red purple coloration. *Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found : C, 68.34; H, 5.56. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 2985 (OH), 1724 (CO_2Et), 1631, 1610 (CO).

Ethyl 3-Bromo-3-formyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (III)——To an ice-cooled solution of 3 g. of II in 30 cc. of $CHCl_3$ was added dropwise, with stirring, a solution of 1.9 g. of Br_2 in 20 cc. of $CHCl_3$ over a period of 30 min. After stirring for 1 hr, at room temperature, 30 cc. of H_2O was added to the reaction mixture, the $CHCl_3$ layer was washed successively with H_2O, $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from benzene-petr. benzin to give 2.7 g. (70%) of colorless needles, m.p. 113°. *Anal.* Calcd. for $C_{14}H_{13}O_4Br$: C, 51.71; H, 4.02. Found : C, 51.79; H, 4.06. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1721 (CO_2Et, CO), 1686 (CO).

Ethyl 3-Formyl-4-hydroxy-2-naphthoate (IV)——A solution of 2.3 g. of III in 10 g. of N,N-dimethylaniline was heated on a boiling water bath for 2 hr., and diluted with 70 cc. of AcOEt. The AcOEt solution was washed with dil. HCl and H_2O, dried and evaporated. The residue was recrystallized from EtOH-petr. ether giving 1 g. (60%) of yellow needles, m.p. 90°. An alcoholic $FeCl_3$ solution of this compound gave a red purple color. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.54; H, 4.95. Found : C, 68.46; H, 4.92. IR $\nu_{\max}^{HCl_3}$ cm^{-1} : 3333~2400 (broad) (OH), 1704 (CO_2Et), 1639 (shoulder), 1623 (CO).

3-Hydroxymethyl-4-hydroxy-2-naphthoic Acid γ-Lactone (V)——To a stirred solution of 700 mg. of IV in 45 cc. of EtOH was added dropwise a solution of 700 mg. of $NaBH_4$ in 30 cc. of EtOH. After the reaction mixture was refluxed for 2 hr., the solvent was removed and the residue was extracted with 70 cc. of AcOEt. The AcOEt extract was washed with dil. HCl and H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to give 450 mg. (77%) of colorless needles, m.p. 248° (decomp.). *Anal.* Calcd. for $C_{12}H_8O_3$: C, 71.99; H, 4.03. Found : C, 72.07; H, 3.87.

3-Ethoxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (X)——A mixture of 7.5 g. of diethyl oxalate, EtONa (prepared from 1 g. of Na and 15 cc. of anhyd. EtOH) and 20 cc. of anhyd. benzene was refluxed for a few minutes. To the cooled reaction mixture was added a solution of 4.4 g. of I[2] in 20 cc. of anhyd. benzene, and was stirred in N_2 stream at room temperature for 4 hr. before being allowed to stand over night. To the ice-cooled reaction mixture was added 50 cc. of H_2O and 10 cc. of 2% NaOH. The benzene layer was extracted with 2% NaOH and the alkaline extracts were combined with the aqueous layer. The alkaline solution was acidified with dil. HCl and extracted with AcOEt. The AcOEt extract was washed with H_2O, and dried. Evaporation of the solvent left 5.1 g. of an oily residue which solidified on standing for a while. Recrystallizations from Et_2O-petr. ether gave pale yellow needles, m.p. 146° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86. Found : C, 62.13; H, 4.74. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1718 (CO_2Et), 1706 (CO_2H), 1600 (broad) (CO).

3-Bromo-3-ethoxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (XII)——To a solution of 1.0 g. of X in 50 cc. of $CHCl_3$ was added dropwise a solution of 0.6 g. of Br_2 in 5 cc. of $CHCl_3$ at room temperature. After stirring for further 5 hr. at room temperature, the reaction mixture was washed with H_2O, $NaHCO_3$ solution and, then H_2O, and dried. Evaporation of the solvent gave 0.9 g. of a viscous oil which solidified spontaneously. Recrystallizations from benzene-petr. benzin gave colorless needles, m.p. 156°. *Anal.* Calcd. for $C_{15}H_{13}O_6Br$: C, 48.79; H, 3.55. Found : C, 48.94; H, 3.44. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1754 (CO_2Et), 1721 (CO_2H and CO), 1675 (CO).

Ethyl 3-Ethoxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VII)——To a suspension of 2.5 g. of NaH in 50 cc. of anhyd. Et_2O was added under stirring at room temperature a solution of 13.1 g. of diethyl oxalate in 10 cc. of anhyd. Et_2O and 5 drops of anhyd. EtOH, followed by a solution of 6.5 g. of I in 30 cc. of anhyd. Et_2O. The reaction mixture was stirred for 5 hr., during which time the color of the solution changed from yellow to dark red. To the reaction mixture was added 10 cc. of Et_2O and 15 cc. of H_2O. The separated Et_2O layer was washed with 30 cc. of 2% NaOH. The aqueous layer and the alkaline washings were combined, acidified with dil. HCl and extracted with benzene. The benzene extract was washed with H_2O, $NaHCO_3$ solution and H_2O, and dried. Evaporation of benzene gave 9 g. of VII as a brown oil, IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1718 (CO_2Et), 1597 (broad) (CO). Heating VII over glass wool yielded diethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (VIII), a colorless oil of b.p$_{0.1}$ 148～153°(bath temperature). *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found : C, 65.97; H, 6.40. When a large excess of NaH was used and the reaction time was prolonged (10 hr.) in the condensation of I with diethyl oxalate, a main product was 3-oxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (IX), m.p. 180°(decomp.). *Anal.* Calcd. for $C_{13}H_{10}O_6$: C, 59.54; H, 3.84. Found : C, 59.63; H, 4.17. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1701 (CO_2H), 1590 (broad) (CO).

Ethyl 3-Bromo-3-ethoxalyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (XI)——This was prepared from 6 g. of VII by the same method as that for the preparation of XII, m.p. 75°, yield, 6 g. Recrystallization from benzene-petr. benzin gave colorless needles, m.p. 75.5°. *Anal.* Calcd. for $C_{17}H_{17}O_6Br$: C, 51.40; H, 4.31. Found : C, 51.55; H, 4.34. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1751 (CO_2Et), 1724 (CO_2Et and CO), 1689 (CO).

Monoethyl Ester of 3-Oxalyl-4-hydroxy-2-naphthoic Acid (XIII)——A solution of 200 mg. of the bromide XI and 4 g. of morpholine was stirred at room temperature for 5 hr., and the mixture was poured into dil. HCl. The precipitate was triturated with AcOEt. The AcOEt solution was washed with H_2O, $NaHCO_3$ solution and then H_2O, and condensed, giving only a small amount of viscous oil. The $NaHCO_3$ washings were acidified with dil. HCl, the precipitate was collected and recrystallized from benzene to give 100 mg. of XIII as yellow crystals, m.p. 137～138° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found : C, 62.21; H, 4.17.

When this reaction was carried out at 60～70° employing N,N-dimethylaniline in the place of morpholine, ethyl 4-hydroxy-3-ethoxalyl-2-naphthoate (XVI) was obtained as a main product accompanied with a small amount of XIII. Methylation of XVI with CH_2N_2 and recrystallizations from benzene-petr. benzin of the product gave ethyl 3-ethoxalyl-4-methoxy-2-naphthoate (XVII), as colorless cubes, m.p. 129°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found : C, 65.12; H, 5.58.

Methylation of XIII——A mixture of 290 mg. of XIII, 500 mg. of MeI, 500 mg. of anhyd. K_2CO_3 and 40 cc. of anhyd. Me_2CO was refluxed for 20 hr. After cooling, the inorganic materials were filtered and washed with Me_2CO. The filtrate and washings were combined and evaporated. The residue was taken up in AcOEt, the AcOEt solution was washed with $NaHCO_3$ solution, dil. NaOH and H_2O, and dried over $MgSO_4$. Evaporation of AcOEt gave 190 mg. of crude 3-oxalyl-4-methoxy-2-naphthoic acid methyl ethyl ester (XIV). Recrystallizations from benzene gave colorless needles, m.p. 151°. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found : C, 64.49; H, 5.42.

3-(Carboxyhydroxymethyl)-4-methoxy-2-naphthoic Acid γ-Lactone (XV)——To a suspension of 100 mg. of XIV in 30 cc. of H_2O was added 30 mg. of $NaBH_4$, and the mixture was stirred at 50～60° for 5 hr. After cooling, the resulting yellow clear solution was acidified with dil. HCl, and extracted with AcOEt. The extract was washed with H_2O, dried and evaporated. The residue was recrystallized from benzene, giving 40 mg. of colorless needles, m.p. 193～196°. The melting point of this compound was raised up to 198° by further recrystallizations from benzene. *Anal.* Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found : C, 65.43; H, 3.84. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1780 (lactone), 1733 (CO_2H). This compound was shown to be identical with XV[1)] obtained from 3-(1-hydroxy-2-trichloroethyl)-4-methoxy-2-naphthoic acid γ-lactone by direct comparison of their IR spectra and mixed melting point determination.

3-Hydroxymethyl-4-methoxy-2-naphthoic Acid γ-Lactone (VI)[1)]——a) Prepared from XV according to the method described in the previous paper,[1)] m.p. 168°. IR : $\nu_{\max}^{\text{CHCl}_3}$ 1757 cm^{-1} (γ-lactone).

b) To a solution of 200 mg. of V in 50 cc. of AcOEt was added an Et_2O solution containing a large excess of CH_2N_2, and the reaction mixture was allowed to stand for 40 hr. in an ice box. After adding glacial AcOH to destroy the excess of CH_2N_2, the reaction mixture was washed successively with H_2O, saturated $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from benzene to give 150 mg. (70%) of colorless, m.p. 169°. *Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found : C, 73.22; H, 4.82. IR : $\nu_{\max}^{\text{CHCl}_3}$ 1754 cm^{-1} (lactone). Both samples of VI obtained in a) and b) were shown to be identical by a mixed melting point determination and comparison of their IR spectra.

Summary

As exploratory experiments for the synthesis of 3-hydroxymethyl-4,5,7-trimethoxy-2-naphthoic acid γ-lactone in the course of synthethic studies on α-sorigenin, the synthesis of 3-hydroxymethyl-4-methoxy-2-naphthoic acid γ-lactone (VI) was accomplished by the two routes shown in Chart 1 and 2.

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