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151. Zen-ichi Horii, Takefumi Momose, and Yasumitsu Tamura : Studies on Oxytetracycline and Related Compounds. XVI.*2 Synthesis of 1,3,11-Trimethoxy-5(12*H*)-naphthacenone.

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Terrarubeine,[1] a degradation product of oxytetracycline, has been shown to have a structural formula of 4-dimethylamino-6-methyl-1,3,10,11,12-pentahydroxy-2-napthacenecarboxamide. Recently it has been revealed that aglycones of several glucoside-antibiotics such as pyrromycinones,[2] isorhodomycinones,[3] and aklavinones[4] have a similar naphthacenequinone skeleton with hydroxyl substituents at *peri*-positions. A structural resemblance of these antibiotics is of a great interest from biogenetical, as well as pharmacological point of view. Thus, authors intended to synthesize these antibiotics and their analogues to test their antibacterial activities. The present paper described the preparation of 1,3,11-trimethoxy-5(12*H*)-naphthacenone (I).

Methyl 4-oxo-1,2,3.4-tetrahydro-2-naphthoate (III), prepared by esterification of the corresponding acid (II) with methanol and dry hydrogen chloride in 93% yield, was subjected to base-catalized condensation with 2,4-dimethoxybenzaldehyde. The condensation was carried out by refluxing the reactants with potassium hydroxide in methanol or by stirring them with sodium methoxide in methanol at room temperature, and the yields of 3-(2,4-dimethoxybenzylidene)-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (IV) were 32% in the former case and 47% in the latter. The chalcone-carboxylic acid (IV) was reduced over 5% palladium charcoal under an atmospheric pressure of hydrogen. By interrupting the hydrogenation when one molecular equivalent of hydrogen was absorbed, 3-(2,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (V) was obtained in a quantitative yield, but when the hydrogenation was continued until about two and a half molecular equivalents of hydrogen were absorbed and the speed of absorption was slowered down, the product was a mixture of 3-(2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-naphthoic acid (VI) and the tetralol-derivatives. Another example concerning the behavior of (IV) towards catalytic reduction is the reduction of 2-benzylidene-3,4-dihydro-1(2*H*)-naphthalenone (XX), in which about two and a half molecular equivalents of hydrogen were uptaken for exhaustive hydrogenation while hidrogenation with one molecular equivalent of hydrogen yielded 2-benzyl-3,4-dihydro-1(2*H*)-naphthalenone (XXI).

The ester (VII), obtained by treatment of the acid (V) with diazomethane, was brominated by means of one molecular equivalent of bromine in chloroform or N-bromosuccinimide in boiling carbon tetrachloride, giving a monobromide whose structure was assumed to be methyl 3-(5-bromo-2,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VIII), since it was not dehydrobrominated on treatment with 2,4,6-collidine or lithium chloride in dimethylformamide. Use of two molecular equivalents of bromine in the above bromination reaction resulted in the formation of the dibromide (IX) (74%), which was also prepared from the monobromide (VIII) by further bromination with one mole cular equivalent of bromine in chloroform in 85% yield. Dehydrobromination

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*2 Part XV : This Bullein **9**, 455(1961).

1) F.A. Hochstein, *et al.* : J. Am. Chem. Soc., **75**. 5475 (1953).
2) H. Brockmann and H. Brockmann, Jr. : Naturwiss., **47**, 135 (1960); H. Brockmann and W. Lenk: *ibid.*, **47**, 135 (1960).
3) H. Brockmann and P. Boldt : *Ibid.*, **47**, 134 (1960).
4) J.J. Gordon, *et al.* : Tetrahedron Letters, No. 8, p. 28 (1960); W.D. Ollis, *et al.* : Proc. Chem. Soc., **1960**, 349.

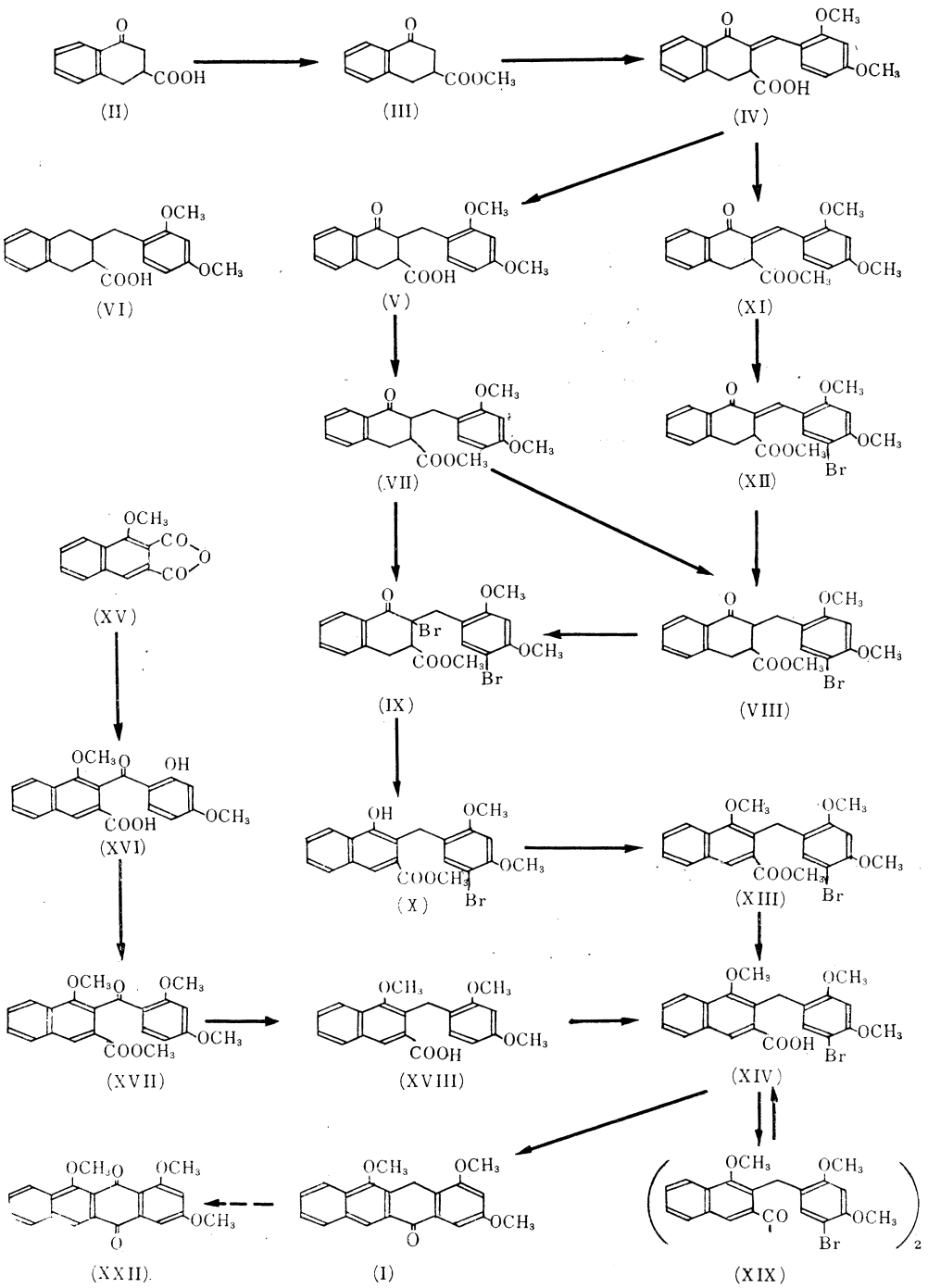

Chart. 1.

of (IX) by heating with morpholine gave methyl 3-(5-bromo-2,4-dimethoxybenzyl)-4-hydroxy-2-naphthoate (X) in 81% yield. The transformation of (IV) to (VIII) by the following reactions would give a further support to the structural assignment for (VIII). Compound (IV) was esterified with diazomethane followed by bromination with bromine in chloro-

form to give, in quantitative yield, methyl 3-(5-bromo-2,4-dimethoxybenzylidene)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (XII), whose structure was assigned by spectral analysis. The catalytic hydrogenation of (XII) over Raney-nickel catalyst gave (VIII), which was shown to be identical with a sample of (VIII) prepared by bromination of (VII).

Methylation of (X) followed by hydrolysis with a potassium hydroxide solution gave 3-(5-bromo-2,4-dimethoxybezyl)-4-methoxy-2-naphthoic acid (XIV) in over-all 85% yield. Compound (XIV) was also prepared starting from 1-methoxy-2,3-naphthalenedicarboxylic anhydride (XV) prepared by the method of Z. Horii.[5] The Friedel-Crafts reaction of (XV) 1,3-dimethoxybenzene followed by methylation with dimethyl sulfate and then reduction with zinc dust in alkaline medium gave 3-(2,4-dimethoxybenzyl)-4-methoxy-2-naphthoic acid (XVIII), which was derived to (XIV) by bromination. Thus, it was proved that in the Friedel-Crafts reaction of (XV) only the carbonyl group located at the *ortho*-position to the methoxy group participated in the reaction.

Refluxing a benzene solution of the acid chloride of (XIV) in the presence of anhyd. stannic chloride resulted in cyclization and simultaneous debromination to afford (I). When this cyclization reaction was carried out at a lower temperature (10°), anhydride, probably (XIX), was obtained instead of (I). Treatment of (XIV) with polyphosphoric acid or conc. sulfuric acid did not effect cyclization. Attempts to oxidize (I) to the corresponding quinone (XXII) were unsuccessful and only the starting material was recovered.

Experimental

Methyl 4-Oxo-1,2,3,4-tetrahydro-2-naphthoate (III)——A solution of 18.7 g. of 4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (II) in 50 g. of anhyd. MeOH was saturated with dry HCl under cooling in an ice-bath, followed by warming at 45° with stirring for 15 min., and then allowed to stand at room temperatnre overnight. The solution was poured onto 150 g. of cracked ice and extracted 5 times with benzene. The combined extracts were washed with saturated $NaHCO_3$ solution and water. After evaporating the solvent, the residual oil was distilled under reduced pressure, giving colorless distillate, b.p_5 166°, which was solidified on standing. Two recrystallizations from petr. ether gave 18.6 g. (93%) of (III), m.p. 32~33°. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.42; H, 6.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1681, 1724.

3-(2,4-Dimethoxybenzylidene)-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (IV)——This condensation was carried out by the following two procedures, (a) and (b). The procedure (b) was found to be preferable to the procedure (a) because of easier separation of the unsaturated keto-acid (IV) from the reaction mixture.

(a) With potassium hydroxide in MeOH[6]: To a stirred solution of 4.5 g. of (III) and 3.3 g. of 2,4-dimethoxybenzaldehyde in 5 cc. of MeOH was added a solution of 1.3g of KOH in 25cc.of MeOH and the mixture was refluxed for 2 hr. After MeOH was removed, the residue was diluted with 2 volumes of water, acidified with conc. HCl and extracted with AcOEt, which was shaken with saturated $NaHCO_3$ solution and the alkaline layer was acidified with conc. HCl. Yellow crystals precipitated were collected, washed 3 times with water, dried and then recrystallized from AcOEt to give 2.2 g. (32%) of yellow crystals, m.p. 177~178° (decomp.). *Anal.* Calcd. for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.13; H, 5.33. IR ν_{max}^{Nujol} cm^{-1}: 1661, 1701.

(b) With MeONa in anhyd. MeOH- To a stirred solution of 5.3 g. of (III) and 4.3 g. 2,4-dimethoxybenzaldehyde in 25 cc. of anhyd. MeOH was added over a period of 30 min. a solution of 12 cc. of anhyd. MeOH containing 0.6 g. of Na. After stirring for an additional 24 hr., the mixture was diluted with 80 cc. of ice-water, acidified with dil. H_2SO_4 and extracted with AcOEt, which was treated similary as described in (a). Crude crystals (5.85 g.) were recrystallized twice from AcOEt, giving 4.15 g. (47%) of yellow crystals, m.p. 177~178° (decomp.), which was not depressed on admixture of a sample of (IV) prepared in (a).

Catalytic Reduction of 3-(2,4-Dimethoxybenzylidene)-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (IV)[7]——Compound (IV) (300 mg.) was dissolved in 20 cc. of anhyd. MeOH and hydrogenated catalytically over 200 mg. of 5% Pd-C at 20° under an atmospheric pressure. The hydrogenation was discontinued when one molecular equivalent of H_2 (20 cc.) was absorbed (10 min.). The catalyst was filtered off

5) Z. Horii, *et al.*: The Bulletin, **10**, 887 (1962).
6) cf. A. Hauser, N. H. Cromwell, S. T. Davis: J. Am. Chem. Soc., **79**, 230 (1957).
7) cf. W. Borsche, P. Hofmann, H. Kühn: Ann., **554**, 23 (1943).

and the filtrate was concentrated. The resulting paste slightly brown-colored was crystallized from dil. EtOH to give 300 mg. (quantitative) of long needles, m.p. 159~160°. Further recrystallizations from dil. EtOH afforded an analytical sample of (V) as colorless needles, m.p. 159~161°. *Anal.* Calcd. for $C_{20}H_{20}O_5$: C, 70.56; H, 5.92. Found : C, 70.71; H, 6.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1684, 1704.

When the above hydrogenation was thoroughly carried out, H_2-uptake amounted to 48 cc. (ca. 2.4 molecular equivalents) (1.5 hr.). From the reduction mixture a small amount of colorless needles of 3-(2,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-naphthoic acid (VI), m.p. 200~205° (from Me_2CO-petr. ether) were separated. *Anal.* Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found : C, 73.39; H, 6.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1700. After a filtration of the catalyst, the solvent was removed from the reduction mixture to give ca. 300 mg. of colorless crystals, m.p. 183~193°. When the crude reduction product of m.p. 183~193° was oxidized by stirring with MnO_2[8] in anhyd. Me_2CO at room temperature for 3 days, the tetralone-carboxylic acid (V) (m.p. 159~161°) was obtained.

Catalytic Reduction of 2-Benzylidene-3,4-dihydro-1(2*H*)-naphthalenone (XX)——According to the same procedure as described in the reduction of (IV), 1.2 g. of (XX) in 20 cc. of anhyd. MeOH was hydrogenated catalytically over 200 mg. of 5% Pd-C and the hydrogenation was discontinued when one molecular equivalent of H_2 (112 cc.) was absorbed. The catalyst was filtered off and the filtrate was evaporated to give 1.2 g. of a half-solid, which was recrystallized from petr. ether to colorless prisms, m.p. 59~62°. The melting point of this material showed no depression when admixed with an authentic sample of (XXI) which was prepared by direct benzylation of 1-tetralone with benzyl chloride in the presence of $NaNH_2$ in boiling toluene. *Anal.* Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found : C, 86.37; H, 6.53. IR ν_{max}^{Nujol} : 1675 cm^{-1}.

When the hydrogenation was thoroughly carried out, 261 cc. or 2.33 molecular eqivalents of H_2 were absorbed. After the catalyst was filtered off, the solvent was removed from the reduction mixture. The residue was recrystallized twice from ether-petr. ether (1:6) to give long needles, m.p. 113°. This material is supposed to be 2-benzyl-1-tetralol (IR ν_{max}^{Nujol} : 3210 cm^{-1}), but has not been further characterized.

Methyl 3-(2,4-Dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VII)——The methylation of (V) with CH_2N_2 afforded the methyl ester (VII) in a quantitative yield. Colorless prisms form MeOH, m.p. 133~135°. *Anal.* Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found : C, 71.38; H, 6.23. IR ν_{max}^{Nujol} cm^{-1} : 1686, 1724.

Methyl 3-(2,4-Dimethoxybenzylidene)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (XI)——Methylation of the keto-acid (3.8 g.) with CH_2N_2 gave 3.8 g. of yellow rhombics, m.p. 145~148°, which was raised up to 147.5~148.5° by two recrystallizations from MeOH. *Anal.* Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found : C, 71.60; H, 5.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1661, 1721.

Methyl 3-(5-Bromo-2,4-dimethoxybenzylidene)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (XII)——To an ice-cooled stirred solution of the unsaturated keto-ester (XI) (700 mg.) in anhyd. $CHCl_3$ (10 cc.) was added dropwise 320 mg. of Br_2 in 10 cc. of anhyd. $CHCl_3$ over a period of 1 hr. and the mixture was stirred at 10~15° for an additional 3 hr. The mixture was treated as usually giving 900 mg. of crude (XI), as crystals of m.p. 158~162°. Recrystallization from Me_2CO-MeOH gave yellow rhombics, m.p. 164~165°. *Anal.*Calcd. for $C_{21}H_{19}O_5Br$: C, 58.48; H, 4.44. Found : C, 58.79; H, 4.42. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1662, 1724.

Methyl 3-(5-Bromo-2,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VIII)——(a) From (VII) : To a stirred solution of 300 mg. of (VII) in 10 cc. of anhyd. $CHCl_3$ was added slowly 0.13 g. of Br_2 in 3 cc. of anhyd. $CHCl_3$ under cooling with ice over a period of 1 hr. and stirred at room temperature for an additional 3 hr. After washing with 2% NaOH and water, the solution was dried over Na_2SO_4 and evaporated. The residual paste (0.4 g.) was triturated with Et_2O giving 120 mg. of crude crystalline (VIII), which was recrystallized several times from Me_2CO-H_2O to m.p. 180~182°. *Anal.* Calcd. for $C_{21}H_{21}O_5Br$: C, 58.20; H, 4.88; Br, 18.44. Found : C, 57.78; H, 4.96; Br, 18.84. IR ν_{max}^{Nujol} cm^{-1} : 1681, 1724.

Bromination of (VII) with N-bromosuccindmide in the presence of benzoyl peroxidein boiling CCl_4 gave also (VIII).

(b) From (XII) : A solution of 200 mg. of (XII) in 20 cc. of freshly distilled dioxane was hydrogenated over 1 g. of Raney-Ni under an atmospheric pressure of H_2. The hydrogenation was discontinued when absorption of H_2 amounted to 12 cc. (1.15 mol.). The catalyst was filtered off from the reduction mixture and the filtrate was evaporated to give 300 mg. of slightly brown-colored paste, which afforded 200 mg. of colorless crystals on trituration with Et_2O. Recrystallization from Me_2CO gave colorless rhombic crystals, m.p. 190~191°, which was identified with a sample of (VIII) obtained in (a). IR ν_{max}^{Nujol} cm^{-1} : 1680, 1723.

Methyl 3-Bromo-3-(5-bromo-2,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (IX)——(a) Bromination of the ketoester (VII) : To an ice-cooled stirred solution of 3.3 g. of (VII) in 50 cc. of anhyd. $CHCl_3$ was added dropwise a solution of 3 g. of Br_2 in 30 cc. of anhyd. $CHCl_3$ over a period

8) J. Attenburrow, *et al.* : J. Chem. Soc., **1952**, 1094; cf. R.M. Evans : Proc. Chem. Soc., **1958**, 47.

of 1.5 hr., and the mixture was stirred at room temperature for an additional 5 hr. The mixture was washed successively with 2% NaOH and water, dried over Na_2SO_4 and evaporated to give 4.8 g. of slightly brown-colored half solid, which was triturated with Et_2O giving colorless crystals, m.p. 167~170°. An analytical sample, m.p. 170~172° (colorless needles), was prepared by two recrystallizations from Me_2CO-H_2O. *Anal.* Calcd. for $C_{21}H_{20}O_5Br_2$: C, 49.24; H, 3.94; Br, 31.21. Found: C, 49.38; H, 3.98; Br, 31.70. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1730.

(b) Bromination of the monobromide (Ⅷ): To a stirred solution of 50 mg. of the monobromide (Ⅷ) in 10 cc. of anhyd. $CHCl_3$ was added dropwise 40 mg. of Br_2 in 10 cc. of anhyd. $CHCl_3$ over a period of 2 hr., and the mixture was stirred at room temperature for an additional 2 hr. The reaction mixture was washed successively with water, 2% NaOH and water, dried over Na_2SO_4 and evaporated. A half solid (50 mg.) thus obtained was triturated with Et_2O giving colorless needles, m.p. 166~169°. Two recrystallizations from Me_2CO-H_2O gave colorless needles, m.p. 170~172°, which was not depressed on admixture with a sample of (Ⅸ) obtained in (a).

Methyl 3-(5-Bromo-2,4-dimethoxybenzyl)-4-hydroxy-2-naphthoate (X)——A solution of 6.6 g. of the dibromide (Ⅸ) in 22.6 g. of freshly distilled morpholine[6] was heated on a steambath for 5 hr. To the reaction mixture was added two volumes of Et_2O, and the separated morpholin hydrobromide (ca. 2.1 g.) was filtered off. The filtrate was washed with water until the washings became neutral to lithmus and dried over Na_2SO_4. Removal of the solvent gave 6.3 g. (81% yield) of crystals, m.p. 158~162°. Two recrystallizations from Me_2CO-H_2O gave colorless microleaflets, m.p. 162~163°, which showed a positive Beilstein test. *Anal.* Calcd. for $C_{21}H_{19}O_5Br$: C, 58.48; H, 4.44. Found: C, 58.55; H, 4.58. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708, 3356.

Methyl 3-(5-Bromo-2,4-dimethoxybenzyl)-4-methoxy-2-naphthoate (XIII)——A mixture of 3.1 g. of the naphthol (X), 10 g. of MeI and 10 g. of anhyd. K_2CO_3 in 20 cc. of dry Me_2CO was refluxed for 19 hr. After removing inorganic salts, the filtrate was concentrated to dryness and the residue was dissolved in Me_2CO. Removal of the solvent gave 3.4 g. of crude crystals, which were purified by two recrystallizations from Me_2CO-H_2O to colorless prisms, m.p. 138~139°. *Anal.* Calcd. for $C_{22}H_{21}O_5Br$: C, 59.33; H, 4.75. Found: C, 59.39; H, 4.82. IR $\nu_{max}^{CHCl_3}$: 1723 cm^{-1}.

3-(2-Hydroxy-4-methoxybenzoyl)-4-methoxy-2-naphthoic Acid (XVI)——To a solution of 260 mg. (1.9 mmole) of 1,3-dimethoxybenzene and 300 mg. (2.3 mmole) of anhyd. $AlCl_3$ in 50 cc. of nitrobenzene was added gradually a solution of 400 mg. (1.8 mmole) of 1-methoxy-2,3-naphthalenedicarboxylic anhydride (XV)[5] in nitrobenzene. The mixture was heated at 80~90° for 2 hr., allowed to stand overnight at room temperature and then poured into ice-conc. HCl. The whole mixture was subjected to steam-distillation to remove nitrobenzene. An oily residue of steam-distillation was extracted repeatedly with hot 10% Na_2CO_3. The combined extracts were acidified and extracted with AcOEt, which was washed with water and dried over Na_2SO_4. After an evaporation of the solvent, the residue was recrystallized from AcOEt-petr. ether, giving 100 mg. (16.2%) of the keto-acid (XVI), m.p. 228~229°. This compound gave a positive $FeCl_3$ test (purplish brown). *Anal.* Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 67.77; H, 4.51. IR ν_{max}^{Nujol} cm^{-1}: 1629, 1689.

Methyl 3-(2,4-Dimethoxybenzoyl)-4-methoxy-2-naphthoate (XVII)——A mixture of 100 mg. (0.29 mmole) of (XVI), 2 g. (14.1 mmole) of MeI, 3 cc. of dry Me_2CO and 1 g. of anhyd. K_2CO_3 was refluxed for 22 hr., during which time a small portion of MeI was added every 6 hr. After removing the solvent, the residue was treated with H_2O, acidified and extracted with AcOEt, which was washed with water, dried over Na_2SO_4 and evaporated. The residue was treated with Et_2O and the crystals obtained were recrystallized from AcOEt giving 100 mg. (90%) of (XVII), m.p. 128~129°. *Anal.* Calcd. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.37; H, 5.05. IR ν_{max}^{Nujol} cm^{-1}: 1645, 1704.

3-(2,4-Dimethoxybenzyl)-4-methoxy-2-naphthoic Acid (XVIII)——One gram of Zn dust, which was washed successively with 3% HCl, distilled water and EtOH, was added to 1 cc. of ammoniacal $CuSO_4$ solution prepared by combining 2*N* NH_4OH and 2*N* $CuSO_4$. This mixture was added to a suspension of 600 mg. (1.6 mmole) of (XVII) in 20 cc. of 2*N* NaOH and refluxed for 50 hr. The reaction mixture was cooled and acidified. The precipitates deposited were collected, washed with water and recrystallized from AcOEt to give 500 mg. (90%) of colorless needles, m.p. 160~161°. *Anal.* Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.74; H, 5.74. IR ν_{max}^{Nujol} cm^{-1}: 1686.

3-(5-Bromo-2,4-dimethoxybenzyl)-4-methoxy-2-naphthoic Acid (XIV)——(a) Alkaline hydrolysis of the ester (XIII): A mixture of 1.3 g. of the ester (XIII), 20 cc. of MeOH, 0.4 g. of KOH and 15 cc. of water was refluxed for 24 hr. The cooled mixture was acidified with ice-10% H_2SO_4 and extracted three times with AcOEt. The combined extracts were washed three times with water and then extracted thoroughly (about thirty times) with 20 cc. each of saturated Na_2CO_3. After washing once with AcOEt and twice with Et_2O, the combined alkaline extracts were acidified with 10% H_2SO_4 and extracted three times with AcOEt. The AcOEt extract was washed with water and dried over Na_2SO_4. The solvent was evaporated and 1.2 g. of residual crude crystals were recrystallized twice from Me_2CO-H_2O to give 1.1 g. (87%) of colorless needles, m.p. 180~182°. *Anal.* Calcd. for $C_{21}H_{19}O_5Br$: C, 58.48; H, 4.44. Found: C, 58.75; H, 4.50. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1692, 2618 (broad). This acid is sparingly soluble in

saturated $NaHCO_3$ solution. On alternative hydrolyses using either water or MeOH alone as a solvent, the starting material was recovered after 24 hr's refluxing.

(b) Bromination of (XVIII): To an ice-cooled solution of 222.7 mg. (0.641 mmole) of (XVIII) in 10 cc. of $CHCl_3$ was added with stirring a solution of 120.9 mg. (0.673 mmole) of Br_2 in 10 cc. of $CHCl_3$ and the mixture was stirred at room temperature for 30 min. after the addition was completed. The mixture was washed successively with $Na_2S_2O_4$ solution and water, dried over Na_2SO_4 and evaporated. The residue was recrysrallized from AcOEt and then from Me_2CO-H_2O to give 250 mg. (90%) of colorless crystals, m.p. 178~181°, which was identified with a sample of (XIV) prepared in the above section (a) by mixed melting point determination and a comparison of IR spectra. *Anal.* Calcd. for $C_{21}H_{19}O_5Br$: C, 58.48; H, 4.44; Br, 18.53. Found: C, 58.92; H, 4.78; Br, 18.89.

Cyclization of (XIV) to 1,3,11-Trimethoxy-5(12*H*)-naphthacenone (I)——A solution of 200 mg. of the acid (XIV) and 100 mg. of PCl_5 in 5 cc. of anhyd. benzene was heated at 50° for 10 min. To the acid chloride solution obtained was added rapidly 2 cc. of freshly distilled anhyd. $SnCl_4$ in 2 cc. of anhyd. benzene. The brownish orange emulsion thus obtained was stirred at 10° for 20 min. and then refluxed for an additional 5 min., cooled immediately and treated with ice-10% H_2SO_4. The benzene layer was separated and the aqeous layer was extracted three times with AcOEt. The benzene layer and the AcOEt extracts were combined and washed successively five times with 10% H_2SO_4 to remove Sn^{4+}, and then three times with water and with saturated $NaHCO_3$ solution to remove the acid (XIV). On the treatment with $NaHCO_3$ solution, the organic layer changed its color from dark blue to orange-red. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to give 100 mg. of red needles, m.p. 175~179°. The crude crystals were recrystallized three times from Me_2CO-H_2O to pinkcolored needles, m.p. 180~182°, which showed negative Beilstein test and negative halogen test on fusion with Na. *Anal.* Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.60; H, 5.46. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1653.

In other runs in which the cyclization with $SnCl_4$ was carried out at 10° for 20 min, either in-dry benzene or in dry CS_2, none of the cyclized product had been obtained except 100 mg. of colorless microprisms, m.p. 199~200°(after two recrystallizations from Me_2CO) and 80 mg. of the acid (XIV). The compound of m.p. 199~200° showed a positive Beilstein test, was insoluble in aqueous Na_2CO_3 and sparingly soluble in usual organic solvents. Its IR spectrum (in Nujol) shows characteristic absorption bands due to anhydride carbonyl group (open-chain, conjugated) at 1779 and 1718 cm^{-1}. *Anal.* Calcd. for $C_{42}H_{36}O_9Br_2$: C, 59.73; H, 4.30. Found: C, 60.04; H, 4.44.

This anhydride (100 mg.) was hydrolyzed to the acid (XIV) in 88% yield by refluxing with a mixture of 5 cc. of dioxane, 100 mg. of KOH and 5 cc. of water for 30 min.

Summary

The Stobbe condensation of methyl 4-oxo-1,2,3,4-tetrahydro-2-naphthoate (III) with 2,4-dimethoxybenzaldehyde gave the chalconecarboxylic acid (IV), which was derived to 3-(5-bromo-2,4-dimethoxybenzyl)-4-methoxy-2-naphthoic acid (XIV) by 6 steps. The compound (XIV) was also prepared from 1-methoxy-2,3-naphthalenedicarboxylic anhydride (XV) by 4 steps. Cyclization reaction of (XIV) employing stannic chloride as a condensing agent resulted in a replacement of bromine atom substituted in the nucleus with hydrogen to form 1,3,11-trimethoxy-5(12*H*)-naphthacenone (I). The whole reaction schema was illustrated in Chart 1.

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