give 0.2 g. of bright yellow crystals, m.p. 270～275°. Four recrystallizations from acetone gave 0.13 g. of Ⅻ as yellow short needles. m.p. 275～278°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1663 (C=O), 1620, 1584, 1570 (arom.). *Anal.* Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found: C, 72.58; H, 4.52.

Summary

The Friedel-Crafts condensation of 3,6-dimethoxyphthalic anhydride (Ⅱ) with methyl 2-ethyl-5-hydroxy-1-naphthoate (Ⅲ) gave 2-ethyl-5-hydroxy-6-(2-carboxy-3,6-dimethoxybenzoyl)-1-naphthoate (Ⅳ), a key intermediate for the synthesis of η-pyrromycinone (I, R=H). An attempt to cyclize Ⅳ to η-pyrromycinone dimethyl ether (I, $R=CH_3$), however, resulted in formation of 9-ethyl-1,6-dihydroxy-4-methoxynaphthacenequinone (Ⅴ). The structure of Ⅴ was confirmed by alternative synthesis.

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Synthetic Studies on η-Pyrromycinone. Ⅳ.[*1] Conversion of 1,11-Dimethoxy-5(12*H*)-naphthacenones into 4,6-Dimethoxynaphthacenequinones by Chromium Trioxide Oxidation.

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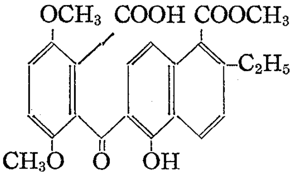
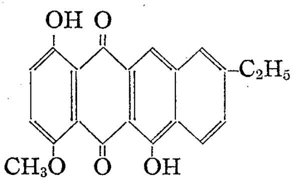
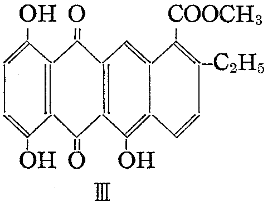
In the preceding paper,[*1] it has been reported that the cyclization of methyl 2-ethyl-5-hydroxy-6-(2-carboxy-3,6-dimethoxybenzoyl)-1-naphthoate (I) resulted in the removal of methoxycarbonyl group, giving only 2-ethyl-4-methoxy-1,6-dihydroxynaphthacenequinone (Ⅱ) and no compound holding a carboxyl function. The present work was undertaken to investigate an alternative route to η-pyrromycinone (Ⅲ) derivative from I. One route which appears promising is *via* 5(12*H*)-naphthacenone derivative (Ⅳ). The cyclization of I to Ⅳ would not require such a drastic condition as employed for the direct cyclization[*1] of I.



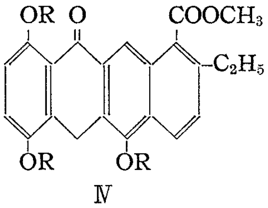
I



Ⅱ



Ⅲ

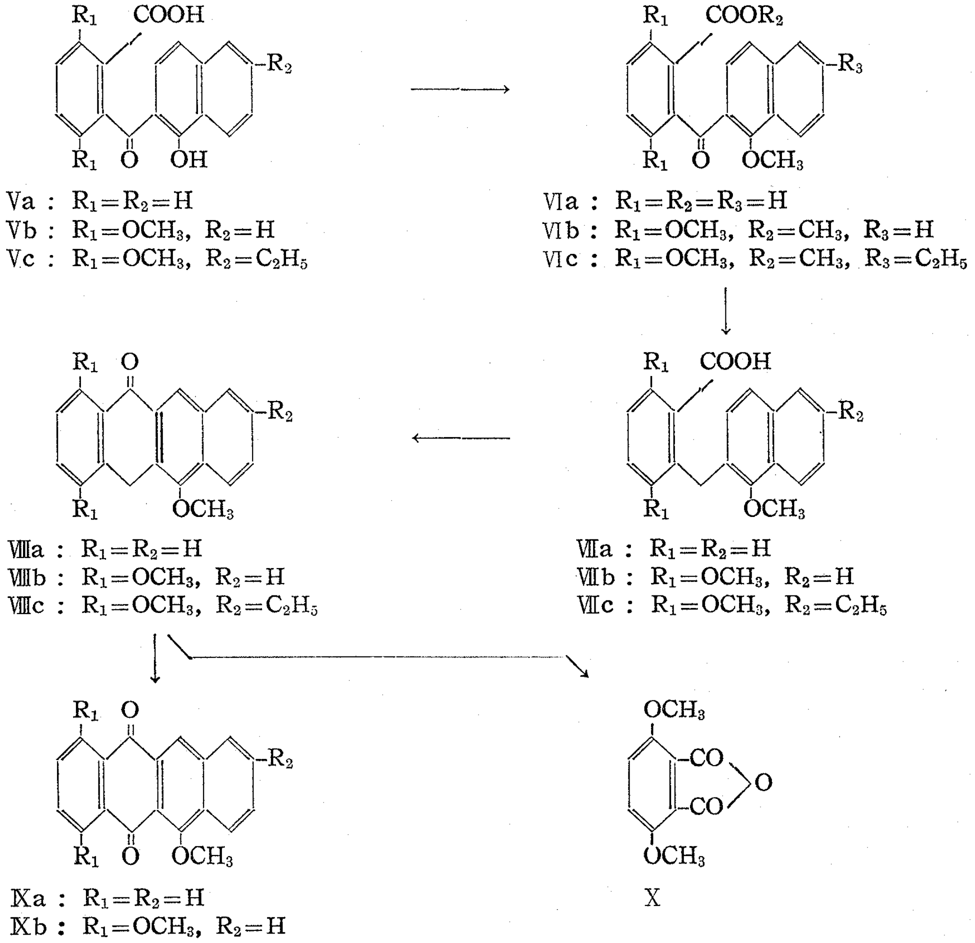


Ⅳ

[*1] Part Ⅲ. Z. Horii, T. Momose, Y. Tamura: This Bulletin, **13**, 737 (1954).

[*2] Toneyama, Toyonaka, Osaka-fu (堀井善一, 百瀬雄章, 田村恭光).

However, a difficulty might be encountered[1] with the subsequent oxidation step to the quinone derivative. Therefore, 11-methoxy-5(12*H*)-naphthacenones (VIIIa, b and c) were selected as model compounds, and their oxidation to the corresponding naphthacenequinones (IXa, b and c) was investigated. An oxidation employing a large excess of chromium trioxide and a shorter reaction time than usual gave a satisfactory result.



Va : $R_1=R_2=H$
Vb : $R_1=OCH_3$, $R_2=H$
Vc : $R_1=OCH_3$, $R_2=C_2H_5$

VIa : $R_1=R_2=R_3=H$
VIb : $R_1=OCH_3$, $R_2=CH_3$, $R_3=H$
VIc : $R_1=OCH_3$, $R_2=CH_3$, $R_3=C_2H_5$

VIIa : $R_1=R_2=H$
VIIb : $R_1=OCH_3$, $R_2=H$
VIIc : $R_1=OCH_3$, $R_2=C_2H_5$

VIIIa : $R_1=R_2=H$
VIIIb : $R_1=OCH_3$, $R_2=H$
VIIIc : $R_1=OCH_3$, $R_2=C_2H_5$

IXa : $R_1=R_2=H$
IXb : $R_1=OCH_3$, $R_2=H$
IXc : $R_1=OCH_3$, $R_2=C_2H_2$

X

Chart 1.

o-(1-Hydroxy-2-naphthoyl)benzoic acid (Va),[2] 6-(1-hydroxy-2-naphthoyl)-2,5-dimethoxybenzoic acid (Vb)*[1] and 6-(6-ethyl-1-hydroxy-2-naphthoyl)-2,5-dimethoxybenzoic acid (Vc)*[1] were methylated with dimethyl sulfate in aqueous potassium hydroxide to give *o*-(1-methoxy-2-naphthoyl)benzoic acid (VIa), methyl 6-(1-methoxy-2-naphthoyl)-2,5-dimethoxybenzoate (VIb), and methyl 6-(6-ethyl-1-methoxy-2-naphthoyl)-2,5-dimethoxybenzoate (VIc), in 59, 65 and 87% yields, respectively. The formations of the esters, Vb and Vc, in such a strong alkaline condition would suggest that their carboxyl groups are sterically hindered. Refluxing VIa, VIb and VIc with zinc powder in aqueous sodium hydroxide gave *o*-(1-methoxy-2-naphthylmethyl)benzoic acid (VIIa), 6-(1-methoxy-2-naphthylmethyl)-2,5-dimethoxybenzoic acid (VIIb), and 6-(6-ethyl-1-methoxy-2-naphthylmethyl)-2,5-dimethoxybenzoic acid (VIIc), in 88, 93 and 97% yields, respectively. Cyclization of VIIa was effected by refluxing with anhydrous zinc chloride in an acetic anhydride-glacial acetic acid mixture in 36% yield, and by heating with polyphosphoric acid at 100° in 71% yield, to give 11-methoxy-5(12*H*)-naphthacenone (VIIIa), which was

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1) Z. Horii, T. Momose, Y. Tamura : This Bulletin, **10**, 946 (1962).
2) C. Deichler, C. Weizmann : Ber., **36**, 547 (1903).

proved to be identical with the reduction product of 6-methoxynaphthacenequinone (Ⅸa) with sodium hydrosulfite in an alkaline medium.[3] Therefore, the polyphosphoric acid cyclization procedure was employed for preparing 1,4,11-trimethoxy-5(12*H*)-naphthacenone (Ⅷb) and 8-ethyl-1,4,11-trimethoxy-5(12*H*)-naphthacenone (Ⅷc) from Ⅶb and Ⅶc, and the cyclizations were achieved in the yields of 88% and 8%, respectively.

In previous paper,[1] it was described that the oxidation of 1,3,11-trimethoxy-5(12*H*)--naphthacenone to the corresponding naphthacenequinone was attempted by a usual manner[4,5] employing chromium trioxide in acetic acid, but it proved unsuccessful. This seems to be ascribed to a steric hindrance of two peri-substituted methoxyl groups to the methylene bridge. Since the methylene moieties of compounds (Ⅷb) and (Ⅷc) are in similar circumstances and, in addition, Ⅷb and Ⅷc are not so stable*[3] in solution, some difficulties would be expected in their oxidation to the corresponding quinones. Examination of reaction conditions, mainly the molar ratio of the oxidizing reagent and the reaction time, enables us to get a 10% yield of 1,4,6-trimethoxynaphthacenequinone (Ⅸb) by standing a solution of Ⅷb and 5 molar equivalents of chromium trioxide in acetic acid at room temperature for 5 hours. Initial attempt employing one molar equivalent of the oxidant at room temperature and a reaction time of 15 hours failed to get a detectable amount of the quinone, and another attempt employing a large excess of the oxidant and the same reaction period resulted in formation of 3,6-dimethoxyphthalic anhydride without quinone. Consequently, Ⅷc was oxidized with 5 molar equivalents of chromium trioxide for one hour to Ⅸc in 12% yield, and Ⅷa with 4 molar equivalents for 5 hours to Ⅸa in 48% yield.

Experimental*[4]

***o*-(1-Methoxy-2-naphthoyl)benzoic Acid (VIa)**——To a stirred mixture of 6.0 g. of *o*-(1-hydroxy-2-naphthoyl)benzoic acid (Va)[2] and 10.4 g. of $(CH_3)_2SO_4$ was added under cooling a solution of 10 g. of KOH in 20 ml. of H_2O, and the mixture was stirred at room temperature for 30 min. and subsequently at 100° for 30 min. After cooling, the inorganic salt was filtered, washed with 20 ml. of H_2O. The filtrate and washing were combined and acidified with 20% H_2SO_4 to give 5.0 g. of precipitates. Recrystallization from 50 ml. of benzene gave 3.7 g. (58.8%) of Ⅵa as colorless needles, m.p. 182~185°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1675 (C=O), 1646 (C=O). *Anal.* Calcd. for $C_{19}H_{14}O_4$: C, 74.45; H, 4.60. Found: C, 74.32; H, 4.45.

Methyl 6-(1-Methoxy-2-naphthoyl)-2,5-dimethoxybenzoate (VIb)——A) With dimethyl sulfate in aqueous sodium hydroxide: To a stirred mixture of 1.0 g. of 6-(1-hydroxy-2-naphthoyl)-2,5-dimethoxybenzoic acid (Vb)*[1] and 20 g. of $(CH_3)_2SO_4$ was added dropwise a solution of 15 g. of NaOH and 30 ml. of H_2O, and the mixture was stirred at 100° for 30 min. After cooling, the mixture was extracted with ether, the extract was washed with satd. aq. NaCl, dried over anhyd. Na_2SO_4 and evaporated to give 0.7 g. (65%) of Ⅵb, m.p. 163~165°. Recrystallization from MeOH-H_2O gave an analytical sample as colorless needles, m.p. 165~166.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1725 (C=O), 1640 (C=O). *Anal.* Calcd. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.33; H, 5.21.

B) With methyl iodide-potassium carbonate in acetone: A mixture of 50 mg. of Vb, 15 ml. of CH_3I, 5 g. of anhyd. K_2CO_3 and 20 ml. of dry acetone was refluxed for 6 hr., during whose time the initial yellow color of the mixture gradually disappeared. After removing acetone, the residue was extracted with hot benzene (50 ml. × 2). The combined extracts were filtered and evaporated to give 40 mg. of colorless crystals, m.p. 164~165°, which was identified wlth the sample of Ⅵb obtained in Section (A) by comparison of their IR spectra in Nujol and mixed melting point determination.

Methyl 6-(6-Ethyl-1-methoxy-2-naphthoyl)-2,5-dimethoxybenzoate (VIc)——6-(6-Ethyl-1-hydroxy-2-naphthoyl)-2,5-dimethoxybenzoic acid*[1] (Vc) (150 mg.) was methylated in a similar manner to that described for Ⅵb in (A) to give 140 mg. of Ⅵc, m.p. 166~168°. Recrystallization from MeOH gave an analytical sample as colorless plates, m.p. 168~170°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1733 (C=O), 1637 (C=O). *Anal.* Calcd. for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92. Found: C, 70.42; H, 6.00.

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*[3] Naphthacenones (Ⅷb) and (Ⅷc) turned dark brown in polar solvents, above all in acidic or hydroxylic one, and were recovered only in a poor yield from these solutions.

*[4] All melting points are uncorrected.

3) Z. Horii, T. Momose, M. Naruse, Y. Tamura: This Bulletin, **10**, 1013 (1962).

4) L. F. Fieser, E. B. Hershberg: J. Am. Chem. Soc., **62**, 49 (1940).

5) M. S. Newman, K. G. Ihrman: *Ibid.* **80**, 3652 (1958).

o-(1-Methoxy-2-naphthylmethyl)benzoic Acid (VIIa)——A suspension of 3.2 g. of VIa, 20 g. of Zn powder (activated with ammoniacal $CuSO_4$) and 20 g. of NaOH in 150 ml. of H_2O was refluxed for 5 hr. Further 20 g. of Zn powder and 20 g. of NaOH were added to the reaction mixture and refluxing was continued for an additional 16 hr. The aqueous layer was decanted while hot and cooled in an ice bath to give precipitates of the Na salt of VIIa, which were collected by filtration. The residual Zn mass was washed with H_2O (100 ml. × 2). The Na salt was dissolved in H_2O, acidified with dil. H_2SO_4 and extracted with ether. The ether extract was washed with satd. aq. NaCl, dried over anhyd. Na_2SO_4 and evaporated. Recrystallization of the residue from benzene gave 1.3 g. of VIIa as colorless micro needles, m.p. 154～156°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1677 (C=O). *Anal.* Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.09; H, 5.47. The alkaline filtrate and the washing of the Zn residue were combined and acidified with conc. HCl to give 1.4 g. of the second crops of VIIa, m.p. 152～154°.

6-(1-Methoxy-2-naphthylmethyl)-2,5-dimethoxybenzoic Acid (VIIb)——To a suspension of 20 g. of Zn powder (activated with ammoniacal $CuSO_4$) and 20 g. of NaOH in 100 ml. of H_2O was added a solution of 0.7 g. of VIb in 15 ml. of EtOH, and the mixture was refluxed for 5 hr. Another 20 g. of Zn powder was added and refluxing continued for 8 hr. Then, further 20 g. of NaOH, 150 ml. of H_2O and 20 g. of Zn powder were added and refluxing was continued for 14 hr. The cooled mixture was decanted, and the residual Zn mass was washed with boiling H_2O (100 ml. × 2). The alkaline layer and the washings were combined, acidified with conc. HCl and extracted with AcOEt. The AcOEt extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 0.65 g. of crystals, m.p. 180～186°. Recrystallization from EtOH-H_2O and then from benzene gave 0.5 g. of VIIb as colorless fine crystals, m.p. 199～201°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3044 (hindered COOH), 1712 (C=O). *Anal.* Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.57; H, 5.48.

6-(6-Ethyl-1-methoxy-2-naphthylmethyl)-2,5-dimethoxybenzoic Acid (VIIc)——Reduction of VIc (140 mg.) in a similar manner to that described for VIIb gave 125 mg. of VIIc as colorless fine crystals, m.p. 202～205°. Recrystallization from benzene gave an analytical sample, m.p. 205～208°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1684 (C=O). *Anal.* Calcd. for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.61; H, 6.18.

11-Methoxy-5(12*H*)-naphthacenone (VIIIa)——A) With anhydrous zinc chloride: A mixture of 0.5 g. of VIIa, 10 ml. of Ac_2O, 10 ml. of AcOH and 20 mg. of anhyd. $ZnCl_2$ was refluxed for 30 min. and poured onto cracked ice. The separtaed oily material was washed with H_2O, satd. aq. $NaHCO_3$ and then H_2O, and triturated with ether to give 100 mg. (35.5%) of pale yellow needles, m.p. 162～164°, which was identified, by mixed melting point determination and spectral comparison, with a sample of VIIIa obtained previously[3] by the reduction of 6-methoxynaphthacenequinone with $Na_2S_2O_4$-NaOH. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1653 (C=O). From the $NaHCO_3$ washing was recovered 0.2 g. of VIIa.

B) With polyphosphoric acid (PPA): A mixture of 0.5 g. of VIIa and 40 g. of PPA was heated with stirring at 100° for 20 min. and poured onto cracked ice. The brownish precipitates were collected, washed with H_2O, satd. aq. $NaHCO_3$ and then H_2O, and dried *in vacuo* to give crystals of m.p. 162～163°. Recrystallization from acetone-H_2O gave 0.1 g. (71%) of pale yellow needles, m.p. 165～167°, which was identified with a sample of VIIIa obtained in (A) by spectral comparison. From the $NaHCO_3$ washing was recovered 0.35 g. of VIIa.

1,4,11-Trimethoxy-5(12*H*)-naphthacenone (VIIIb)——A mixture of 450 mg. of VIIb and 70 g. of PPA was heated at 95～100° for 15 min. and poured onto 100 g. of cracked ice. A similar treatment to that described for VIIIa gave 400 mg. of crystals, m.p. 161～171°, which were recrystallized from acetone to give 350 mg. (87.8%) of VIIIb as pink needles, m.p. 187～192°. Further recrystallization from acetone gave an analytical sample, m.p. 193～196°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1661 (C=O). *Anal.* Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.29; H, 5.21. From the $NaHCO_3$ washing was recovered 30 mg. of VIIb.

8-Ethyl-1,4,11-trimethoxy-5(12*H*)-naphthacenone (VIIIc)——A mixture of 100 mg. of VIIc and 20 g. of PPA was heated at 100° for 20 min. and poured onto 60 g. of cracked ice. A similar treatment to that described for VIIIa gave 95 mg. of crystals, m.p. 137～145°, which were recrystallized twice from acetone and then three times from acetone-cyclohexane (1:4) to give 8 mg. of VIIIc as orangish brown needles, m.p. 159～161°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1652 (C=O). *Anal.* Calcd. for $C_{23}H_{22}O_4 \cdot \frac{1}{3}C_6H_{12}$: C, 76.90; H, 6.71. Found: C, 76.71; H, 6.78.

6-Methoxynaphthacenequinone (IXa)——To an ice-cooled solution of 50 mg. of VIIIa in 10 ml. of AcOH[*5] was added with stirring an ice-cooled solution of 100 mg. of CrO_3 in 10 ml. of AcOH,[*5] and the mixture was allowed to stand at room temperature for 5 hr. Yellow needles began to separate after 1 hr. The mixture was diluted with 5 ml. of ether and filtered. The resulted yellow needles were washed with ether and then three times with H_2O to give 25.5 mg. (49%) of IXa, m.p. 210～212°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1667 (C=O). This sample was identified with an authentic sample[3] by the mixed melting point determination and IR spectral comparison.

1,4,6-Trimethoxynaphthacenequinone (IXb)——To an ice-cooled solution of 50 mg. of VIIIb in 5 ml. of AcOH[*5] was added 100 mg. of CrO_3, and the mixture was stirred at room temperature for 5 hr. The

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[*5] Acetic acid distilled over $KMnO_4$ after 1 hr's refluxing with its 1/10 weight of $KMnO_4$.

mixture was diluted with 50 ml. of $CHCl_3$, washed three times with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give a brown solid, which was immediately subjected to column chromatography on alumina employing $CHCl_3$ as eluent. The first fraction gave 5 mg. of IXb as bright yellow needles. m.p. 270～275°, which were identified with an authentic sample[*1] by the mixed melting point determination and IR spectral comparison.

9-Ethyl-1,4,6-trimethoxynaphthacenequinone (IXc)——To an ice-cooled solution of 78 mg. of VIIIc in 10 ml. of AcOH[*5] was added a solution of 78 mg. of CrO_3 in 3 ml. of AcOH,[*5] and the mixture was allowed to stand at room temperature for 1 hr. The mixture was diluted with 30 ml. of $CHCl_3$ and treated in a similar manner to that described for IXb to give 10 mg. (12.3%) of IXc as bright yellow needles, m.p. 185～189°, which were identified with an authentic sample[*1] by the mixed melting point determination and IR spectral comparison.

Summary

1,11-Dimethoxy-5(12*H*)-naphthacenone derivatives were synthesized, and the successful conversion of them into the corresponding 4,6-dimethoxynaphthacenequinone derivatives by chromium trioxide oxidation was investigated.

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