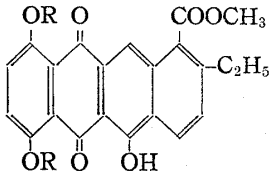
[Chem. Pharm. Bull. 13(6) 737~740 (1965)] UDC 547.682.1.07

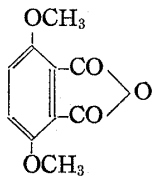
Zen-ichi Horii, Takefumi Momose, and Yasumitsu Tamura : Synthetic Studies on η-Pyrromycinone. III.*1 Intramolecular Cyclization of Methyl 2-Ethyl-5-hydroxy-6-(2-carboxy-3,6-dimethoxybenzoyl)-1-naphthoate.

(*Faculty of Pharmaceutical Sciences, Osaka University**2)

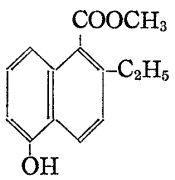
The Friedel-Crafts condensation of 1-naphthol derivative and phthalic anhydride derivative provides a short way to 6-hydroxy-naphthacenequinone derivative, and the cyclization can be effected either by a one-step procedure,[1] that is, fusion with an aluminum chloride-sodium chloride mixture or by a milder two-step procedure[2,3] involving an isolation of an intermediate 2-aroyl-1-naphthol. The latter procedure has now been applied to the condensation of 3,6-dimethoxyphthalic anhydride (II)[4] and methyl 2-ethyl-5-hydroxy-1-naphthoate (III)*1 to η-pyrromycinone dimethyl ether (I, R=CH_3).



I



II



III

The condensation gave methyl 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). However, the cyclization of IV resulted in partial demethylation and simultaneous decarboxylation to yield 4-methoxy-9-ethyl-1,6-dihydroxynaphthacenequinone (V). The present paper describes the Friedel-Crafts condensation of II and III, and also the synthetic confirmation for the structure of the cyclization product (V).

The naphthol (III) was condensed with in boiling acetylene tetrachloride in the presence of anhydrous aluminum chloride to give IV in 40% yield. Cyclization of IV by heating with sulfuric acid or with polyphosphoric acid gave V, which was converted to the trimethyl ether (VI) with methyl iodide and anhydrous potassium carbonate. The structures of the quinones (V) and (VI) were confirmed by their alternative syntheses described below.

6-Ethyl-1-naphthol (VII)*1 was condensed with II in the presence of a small excess of anhydrous aluminum chloride in boiling acetylene tetrachloride to 6-(6-ethyl-1-hydroxy-2-naphthoyl)-2,5-dimethoxybenzoic acid (VIII) in 12% yield, based on VII. The phthaloylnaphthol (VIII) was dissolved in sulfuric acid containing boric acid and heated at 120~130° for 10 min. to give V in 37% yield. Methylation of V with a large excess of methyl iodide and anhydrous potassium carbonate gave quantitatively VI. The monomethoxyquinone structure (V) was proved from its elemental and infrared spectral analyses. The infrared spectrum of VI showed a strong band at 1663 cm^{-1} ascribed to a non-chelated quinone-carbonyl,[3] while V showed no such a band in the 1660~1680

*1 Part II. Z. Horii, T. Momose, Y. Tamura : This Bulletin, **13**, 651 (1965).
*2 Toneyama, Toyonaka, Osaka-fu (堀井善一, 百瀬雄章, 田村恭光).

1) H. Brockmann, W. Müller : Chem. Ber., **92**, 1164 (1959).
2) C. Deichler, C. Weizmann : *Ibid.* **36**, 547 (1903).
3) Z. Horii, T. Momose, M. Naruse, Y. Tamura : This Bulletin, **10**, 1013 (1962).
4) G. D. Graves, R. Adams : J. Am. Chem. Soc., **45**, 2439 (1923). Cf. B. Helferich, H. G. Bodenbender : Ber., **56**, 1113 (1923).

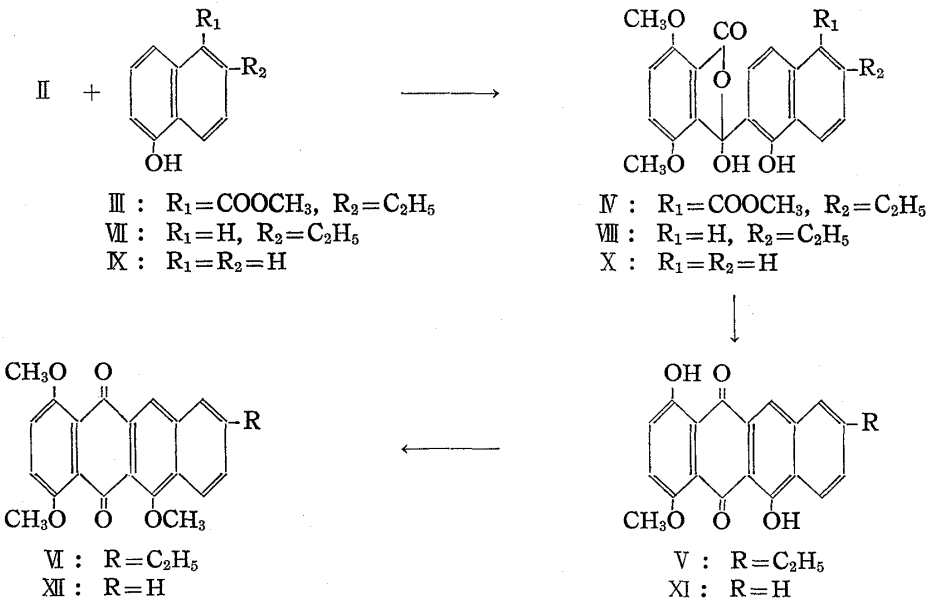


Chart 1.

cm^{-1} region. This demethylation attitude in the cyclization reaction was further exemplified by cyclization of 6-(1-hydroxy-2-naphthoyl)-2,5-dimethoxybenzoic acid (X) prepared by condensation of Ⅱ and α-naphthol (Ⅸ). The cyclization product, 4-methoxy-1,6-dihydroxynaphthacenequinone (Ⅺ), and its methyl ether (Ⅻ) showed similar infrared spectra to those of Ⅴ and Ⅵ, respectively.

Experimental*3

Methyl 2-Ethyl-5-hydroxy-6-(2-carboxy-3,6-dimethoxybenzoyl)-1-naphthoate (IV)——A mixture of 10.4 g. of methyl 2-ethyl-5-hydroxy-1-naphthoate (Ⅲ), 17 g. of 3,6-dimethoxyphthalic anhydride (Ⅱ)[4] (1.8 mol. equiv.) and 250 ml. of $CHCl_2$-$CHCl_2$ was heated with stirring at 140~150° until a clear solution resulted. To the cooled mixture (90°) was added 10 g. (1.7 mol. equiv.) of finely pulverized anhyd. $AlCl_3$ in one portion, and the temperature of the reaction mixture was raised up to 140° during 15 min. and then to 146° during a further 20 min. The reaction mixture was poured onto cracked ice with conc. HCl. The separated solid was crushed in conc. HCl and extracted with AcOEt (200 ml. × 3). The insoluble stuff was collected, which gave 6.8 g. of the anhydride (Ⅱ) on washing with AcOEt. The combined AcOEt extracts were washed with H_2O (30 ml. × 2) and then several times extracted with satd. aq. Na_2CO_3 until no more acidic component was extracted. The Na_2CO_3 layer gave bright yellow precipitates of Na salt of Ⅳ, which were collected, dissolved in H_2O and acidified with dil. H_2SO_4 to give 3.4 g. of pale yellow precipitates. Recrystallization from MeOH gave 2.6 g. of Ⅳ (a pseudo form) as pale yellow crystals, m.p. 183~187°. Further three recrystallizations from MeOH gave an analytical sample of m.p. 188~190°. This compound shows a positive $FeCl_3$ test (green in EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3257 (OH), 1722 (C=O), 1620 (arom. strong); $\nu_{max}^{CHCl_3}$ cm^{-1}: 3279 (OH), 1731 (C=O), 1622 (arom. strong). *Anal.* Calcd. for $C_{24}H_{22}O_8$: C, 65.74; H, 5.06. Found: C, 65.68; H, 5.23.

The alkaline solution separated from the Na salt was shaken with AcOEt (50 ml. × 2), filtered, acidified with dil. H_2SO_4 and extracted with AcOEt (100 ml. × 3). The combined extracts were washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 9.5 g. of a dark brown paste, which was dissolved in $CHCl_3$. Standing the $CHCl_3$ solution caused a precipitation of 2.7 g. of pale brown crystals (assumed to be a decomposition product of Ⅱ from its blue coloration in $FeCl_3$ test*4). The crystals were filtered off, and the filtrate was chromatographed through a column of 120 g. of silica gel with $CHCl_3$ as eluent. The first fraction was concentrated and the residual solid was washed with a small amount of $CHCl_3$ to give 2 g. of the second crops of Ⅳ. The $CHCl_3$ washing was concentrated, and the residue was methylated with CH_3I-K_2CO_3 in acetone and purified through alumina-benzene system to give 1.4 g. of the methyl ether methyl ester of Ⅳ as colorless crystals, m.p. 160~162° (MeOH-H_2O). IR ν_{max}^{Nujol} cm^{-1}: 1723, 1646 (C=O). *Anal.* Calcd. for $C_{26}H_{26}O_8$: C. 66.94; H, 5.62. Found: C, 67.21; H, 5.53.

*3 All melting points are uncorrected.

*4 Acylated naphthols show a green coloration in $FeCl_3$ test.

Cyclization of IV——A) With sulfuric acid : A mixture of 3 g. of H_3BO_3 and 30 ml. of H_2SO_4 was heated at 150° for 5 min. To the cooled mixture was added 0.2 g. of finely pulverized Ⅳ, and the mixture was heated up gradually to 148°*5 and maintained at this temperature for 5 min. A color of the mixture changed from dark red to dark green. The mixture was poured onto 100 g. of cracked ice and extracted with AcOEt (20 ml. × 3). The combined extracts were washed with H_2O and shaken with satd. aq. $NaHCO_3$. Evaporation of the AcOEt layer gave 5 mg. of red needles, m.p. 218～222°, which were proved to be identical with the authentic sample of 4-methoxy-9-ethyl-1,6-dihydroxynaphthacenequinone (Ⅴ) prepared in the later experiment by IR spectral comparison. The starting material, Ⅳ, (50 mg.) was recovered from the alkaline layer.

B) With polyphosphoric acid : A mixture of 0.5 g. of finely pulverized Ⅳ and 50 g. of polyphosphoric acid was heated with stirring at 145～150°*5 for 5 min. The mixture was poured onto 200 g. of cracked ice and treated in a similar manner to that described in A). The AcOEt layer gave 2 mg. of Ⅴ, which was identified with the sample of Ⅴ obtained in A) by IR spectral comparison. From the $NaHCO_3$ layer, no crystalline product could be isolated.

2-(6-Ethyl-1-hydroxy-2-naphthoyl)-3,6-dimethoxybenzoic Acid (VIII)——The Friedel-Crafts condensation of 6-ethyl-1-naphthol*1 (Ⅶ) (2 g.) with Ⅱ (2.5 g.) in the presence of anhyd. $AlCl_3$ (2.5 g.) in $CHCl_2$–$CHCl_2$ (20 ml.) was carried out at 150～155° employing a reaction time of 1 hr. The reaction mixture was poured into dil. HCl and extracted with 300 ml. of AcOEt. The extract was shaken with satd. aq. Na_2CO_3 until no more acidic component was extracted. The alkaline layer gave precipitates of Na salt of Ⅷ, which were collected, dissolved in 15 ml. of H_2O and acidified with 20% H_2SO_4 to give 1.3 g. of pale yellow precipitates. Recrystallization from EtOH (carbon) gave 0.55 g. of Ⅷ (a pseudo form) as pale yellow fine crystals, m.p. 221～223°, which showed a green coloration in $FeCl_3$ test in EtOH. IR ν_{max}^{Nujol} cm^{-1} : 3268 (OH), 1724 (C=O). The EtOH solution of Ⅷ, when standing for several days, separated a normal form as bright yellow prisms, m.p. 221～223°. IR ν_{max}^{Nujol} cm^{-1} : 1730, 1629 (C=O). *Anal.* Calcd. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found : C, 69.43; H, 5.29.

4-Methoxy-9-ethyl-1,6-dihydroxynaphthacenequinone (V)——A mixture of 1 g. of H_3BO_3 and 10 ml. of H_2SO_4 was heated until a clear solution resulted, and cooled to room temperature. To this was added 0.2 g. of finely pulverized Ⅷ, and the mixture was heated with stirring at 120～130° for 10 min. The reaction mixture was poured onto 100 g. of cracked ice and extracted with AcOEt. The extract was washed with satd. aq. $NaHCO_3$ and then H_2O, dried over anhyd. Na_2SO_4 and evaporated to give a reddish brown solid. Extraction of the solid with hot benzene and evaporation of the extract gave 67 mg. of Ⅴ as deep red needles, m.p. 222～224°. IR ν_{max}^{Nujol} cm^{-1} : 1652 (C=O, weak), 1637, 1612, 1585 (arom.). *Anal.* Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found : C, 72.52; H, 4.42.

9-Ethyl-1,4,6-trimethoxynaphthacenequinone (VI)——A mixture of 23 mg. of Ⅳ, 5 g. of anhyd. K_2CO_3, 5 ml. of CH_3I and 20 ml. of acetone was refluxed for 15 hr. After removing acetone, the residue was extracted with $CHCl_3$. The extract was filtered and evaporated to give 20 mg. of bright yellow prisms, m.p. 185～188°. Four recrystallizations from benzene gave 10 mg. of Ⅵ as bright yellow needles, m.p. 189～191°. IR ν_{max}^{Nujol} cm^{-1} : 1663 (C=O), 1626, 1582, 1567 (arom.). *Anal.* Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found : C, 73.64; H, 5.26.

2-(1-Hydroxy-2-naphthoyl)-3,6-dimethoxybenzoic Acid (X)——The Friedel-Crafts reaction of α-naphthol (Ⅸ) (2.1 g.) with Ⅱ (1.5 g.) in the presence of anhyd. $AlCl_3$ (1.5 g.) in $CHCl_2$–$CHCl_2$ (20 ml.) was carried out at 150～155° employing a reaction time of 1 hr. The reaction mixture was poured into dil. HCl and extracted with 300 ml. of AcOEt. The AcOEt extract was shaken with 10% aq. Na_2CO_3 until no more acidic component was extracted. The alkaline layer was shaken twice with AcOEt, filtered, acidified with dil. H_2SO_4 and extracted with AcOEt. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 1.6 g. of a yellowish brown solid. Recrystallization from EtOH gave 1.1 g. (44%) of X (a normal form) as yellow prisms, m.p. 209～211°. Further recrystallization from EtOH gave an analytical sample, m.p. 211～213°. This compound showed a green coloration in $FeCl_3$ test. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1700, 1684 (C=O), 1613 (arom. strong). Recrysrallizations of X (a normal form) from EtOH–H_2O gave crystals of a pseudo form, m.p. 209～211°. IR ν_{max}^{Nujol} cm^{-1} : 3220 (OH), 1727 (C=O), 1616 (arom. strong). *Anal.* Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found : C, 67.95; H, 4.50.

4-Methoxy-1,6-dihydroxynaphthacenequinone (XI)——Cyclization of X (1 g.) was carried out with a mixture of H_3BO_3 (5 g.) and H_2SO_4 (50 ml.) and the reaction mixture treated in a similar manner to that for Ⅷ. The AcOEt layer gave 0.2 g. of deep red needles, m.p. 245～248°, which were sublimed at 210～220°/2 mm. Hg to give 0.18 g. of Ⅺ as deep red needles, m.p. 248～250°. IR ν_{max}^{Nujol} cm^{-1} : 1642 (C=O, weak), 1622, 1612, 1579 (arom.). *Anal.* Calcd. for $C_{19}H_{12}O_5$: C, 71.25; H, 3.78. Found : C, 71.25; H, 3.69.

1,4,6-Trimethoxynaphthacenequinone (XII)——A mixture of 0.2 g. of Ⅺ, 10 g. of anhyd. K_2CO_3, 20 g. of CH_3I and 15 ml. of acetone was refluxed for 16 hr. and treated in a similar manner to that for Ⅵ to

*5 This reaction temperature was determined by the following coloration test : Each a small sample was taken out from the reaction mixture at several stages of reaction temperature, diluted with H_2O and shaken with AcOEt. If the cyclization occured, the AcOEt layer would give a bright yellow coloration due to the resulted quinone.

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 ν_{max}^{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.

(Received March 1, 1965)

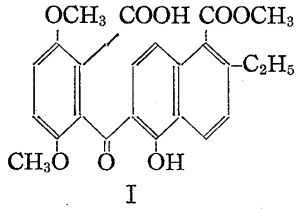
[Chem. Pharm. Bull. 13(6) 740~744 (1965)]

UDC 547.682.1.07

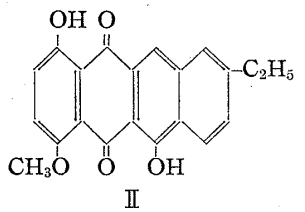
Zen-ichi Horii, Takefumi Momose, and Yasumitsu Tamura: Synthetic Studies on η-Pyrromycinone. IV.*1 Conversion of 1,11-Dimethoxy-5(12*H*)-naphthacenones into 4,6-Dimethoxynaphthacenequinones by Chromium Trioxide Oxidation.

(*Faculty of Pharmaceutical Sciences, Osaka University**2)

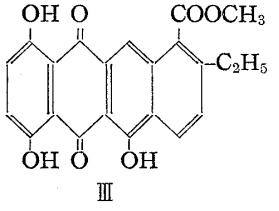
In the preceding paper,*1 it has been reported that the cyclization of methyl 2-ethyl-5-hydroxy-6-(2-carboxy-3,6-dimethoxybenzoyl)-1-naphthoate (I) resulted in the removal of methoxycarbonyl group, giving only 2-ethyl-4-methoxy-1,6-dihydroxynaphthacenequinone (II) and no compound holding a carboxyl function. 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.



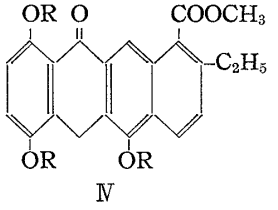
I



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).