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Synthetic Studies on Anthracyclinones. VII.[1] Synthesis of Bisanhydroaklavinone

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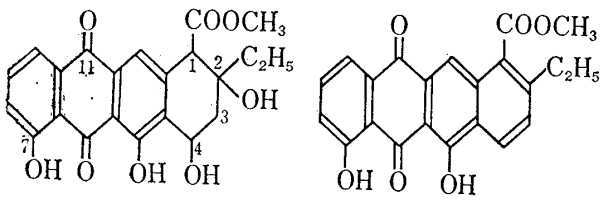
Bisanhydroaklavinone (II) was synthesized by a series of reactions shown in Chart 2. The synthesis provides an unequivocal confirmation for the structure of aklavinone (I).

Aklavinone is the aglycone of aklavin, a pigment antibiotic from the Streptomyces, and was shown, in 1960 by Ollis, *et al.*,[3] to be methyl 2-ethyl-2,4,5,7-tetrahydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-1-naphthacenecarboxylate (I), and converted into the bisanhydro derivative, bisanhydroaklavinone, by dehydration with *p*-toluenesulfonic acid in refluxing toluene.



I II

Chart 1

In recent short communication,[4] there have been reported the synthesis of methyl 2-ethyl-5,7-dihydroxy-6,11-dioxo-6,11-dihydro-1-naphthacenecarboxylate (II) and its identification with bisanhydroaklavinone. The present paper describes a full account of the experiments for the synthesis of II from methyl 2-ethyl-5-hydroxy-6-(2-carboxy-6-methoxybenzoyl)-1-naphthoate (V) prepared by the condensation of methyl 2-ethyl-5-hydroxy-1-naphthoate (IV)[5] with 3-methoxyphthalic anhydride (III).[6] The reactions employed are summarized by the equations shown in Chart 2.

The Friedel-Crafts condensation of III with IV provided, in 17% yield, a product which was only one product isolated and was expected to be V and not to be methyl 2-ethyl-5-hydroxy-6-(2-carboxy-3-methoxybenzoyl)-1-naphthoate (VI), from the fact that the Friedel-Crafts condensation between III and α-naphthol under the same condition as that of the condensation between III and IV gave 3-methoxy-2-(1-hydroxy-2-naphthoyl)benzoic acid (VII) almost exclusively[7] (VII: another isomer=15:1). This was confirmed from the experimental results which would be described below. Methylation of V with methyl iodide and anhydrous potassium carbonate in dry acetone gave methyl 2-ethyl-5-methoxy-6-(2-methoxycarbonyl-6-methoxybenzoyl)-1-naphthoate (VIII), which was reduced by means of zinc powder in boiling aqueous sodium hydroxide to 2-ethyl-5-methoxy-6-(2-carboxy-6-methoxybenzyl)-1-naphthoic acid (IX) in 85% yield.

Cyclization of IX by heating with polyphosphoric acid at 100° for 20 minutes gave methyl 2-ethyl-5,7-dimethoxy-11-oxo-6,11-dihydro-1-naphthacenecarboxylate (X) in 52% yield,

1) Part VI: Z. Horii, H. Hakusui, T. Momose, and E. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **16**, 1251 (1968).
2) Location: *Toneyama, Toyonaka, Osaka-fu.*
3) J.J. Gordon, L.M. Jackman, W.D. Ollis, and I.O. Sutherland, *Tetrahedron Letters*, **1960**, 28.
4) Z. Horii, H. Hakusui, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **14**, 802 (1966).
5) Z. Horii, T. Momose, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 651 (1965).
6) E.D. Amstutz, E.A. Fehnel, and G.R. Neumoyer, *J. Am. Chem. Soc.*, **68**, 349 (1946); see also Part VI of the series.
7) See Part VI of the series.

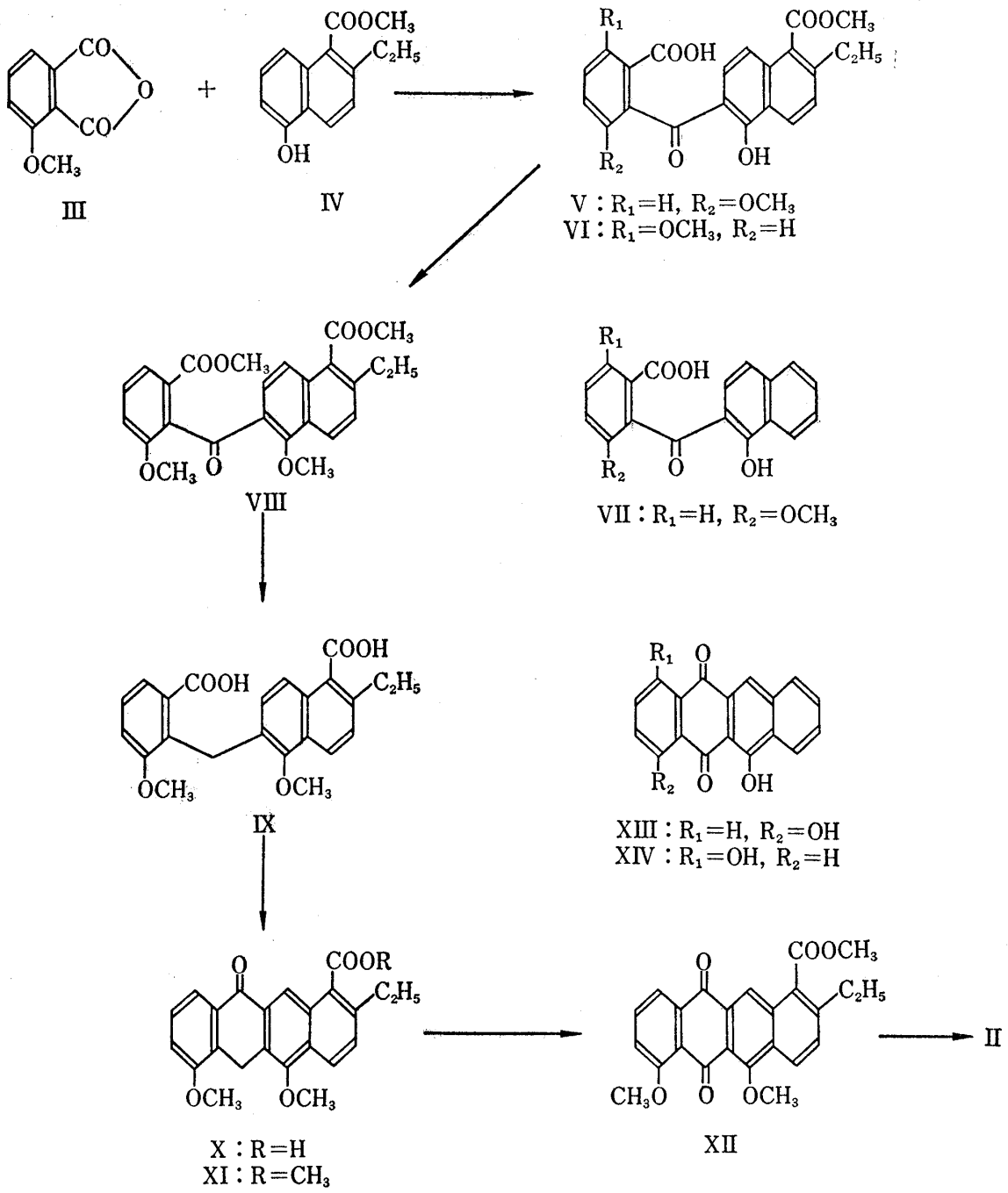


Chart 2

which was methylated with diazomethane to the methyl ester (XI) in 77% yield. Oxidation[8] of XI with 2.5 molar equivalents of chromium trioxide in acetic acid gave methyl 2-ethyl-5,7-dimethoxy-6,11-dioxo-6,11-dihydro-1-naphthacenecarboxylate (XII) in 46% yield. Compound XII corresponds to trimethyl ether of bisanhydroaklavinone. Spectral features of XI and XII are well in agreement with those in conversion of 5(12*H*)-naphthacenones into naphthacenequinones.[8b]

Demethylation[8b] of XII with 13 molar equivalents of boron tribromide in dry methylene chloride at room temperature gave the dihydroxy-quinone-ester (II) in 65% yield.

8) *cf. a*) Z. Horii, T. Momose, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 740 (1965); *b*) *Idem, ibid.*, **13**, 797 (1965).

The structure of II was confirmed from its elemental, infrared spectral and ultraviolet spectral analyses and also by comparison of the spectra with those of model compounds, 1,11-dihydroxynaphthacenequinone (XIII) and 1,6-dihydroxynaphthacenequinone (XIV), which were shown in Fig. 1. The infrared spectrum of II exhibits a strong band at 1672 cm^{-1} which is attributive to a non-chelated quinone carbonyl. This also confirmed that the product derived from the Friedel-Crafts condensation of III with IV was V and not the alternative (VI).

The infrared spectrum of II was exactly superimposed on that of natural bisanhydroaklavinone, and the ultraviolet spectrum and the melting point were also well in agreement with those of natural sourse. This would also give a support to the structure of aklavinone (I).

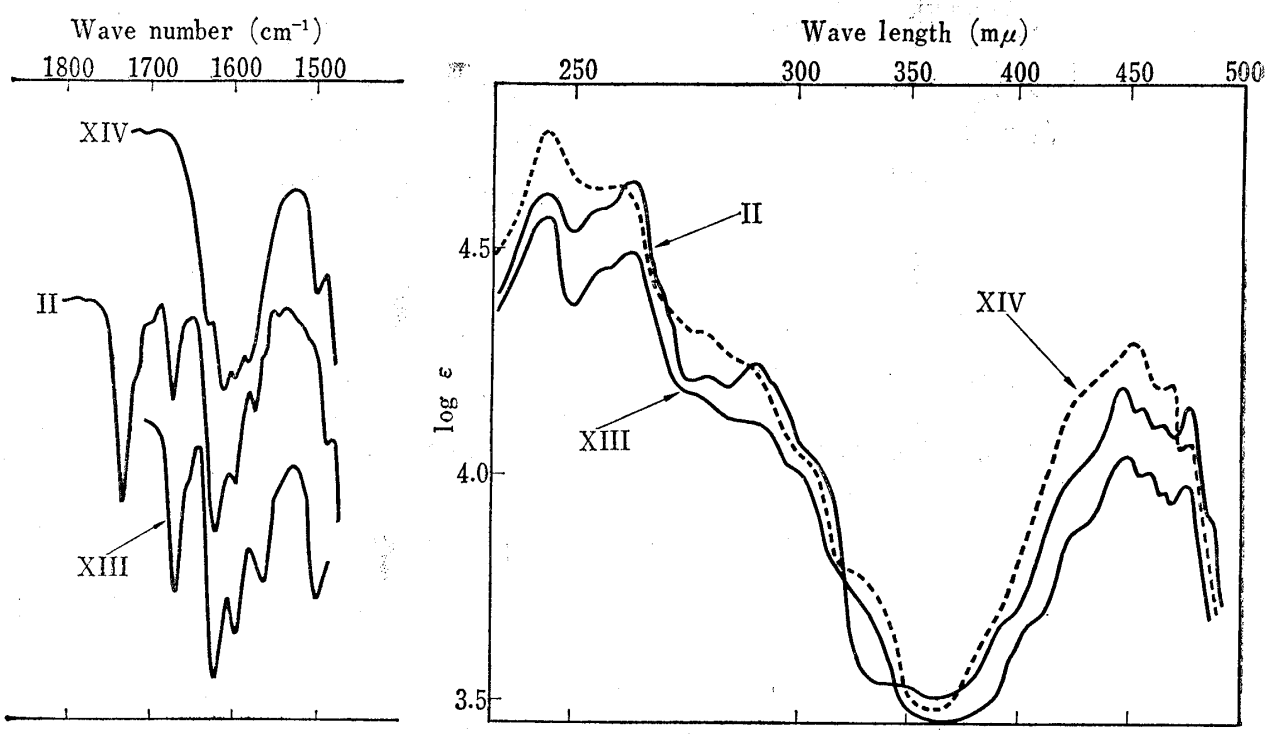


Fig. 1. Infrared (in KBr disk) and Ultraviolet (in *n*-hexane) Spectra of 1,6-Dihydroxy- and 1,11-Dihydroxynaphthacenequinone (XIV and XIII) and Methyl 2-Ethyl-5,7-dihydroxy-6,11-dioxo-6,11-dihydro-1-naphthacenecarboxylate (II)

Experimental[9]

Methyl 2-Ethyl-5-hydroxy-6-(2-carboxy-6-methoxybenzoyl)-1-naphthoate (V)——A mixture of 3-methoxyphthalic anhydride[6] (III) (11 g), methyl 2-ethyl-5-hydroxy-1-naphthoate[5] (IV) (9 g) and dry $CH_2ClCHCl_2$ (200 ml) was heated with stirring at 140—150° until a clear solution resulted. To the cooled solution (90°) was added finely pulverized anhyd. $AlCl_3$ (8.3 g) in one portion, and the temperature of the mixture was raised up to 140° during 15 min and maintained at this temperature for 20 min. The mixture was poured into a mixture of cracked ice and conc. HCl, and the separated solid was crushed in conc. HCl. The whole mixture was extracted with AcOEt (200 ml×3), and the extract was washed with H_2O (30 ml×2) and then exhaustively with saturated. Na_2CO_3 until no more acidic component was extracted. Sodium salt of V deposited from the Na_2CO_3 layer as greenish crystalline precipitates, which were collected, dissolved in H_2O and acidified with dil. H_2SO_4 to give 1.5 g of pale yellow precipitates. The precipitates were proved to consist of a single compound by thin-layer chromatography. Recrystallization of them from benzene gave 1.2 g of V as pale yellow crystals, mp 105—107°. Further three recrystallizations from benzene gave an analytical sample of mp 107°. This compound shows a positive $FeCl_3$ test (green in EtOH). *Anal.* Calcd. for $C_{23}H_{20}O_7 \cdot C_6H_6$: C, 71.59; H, 5.39. Found: C, 71.45; H, 5.32. IR ν_{max}^{KBr} cm^{-1}: 1724, 1689 (C=O), 1623, 1595, 1590 (arom.).

9) All the melting points are uncorrected.

The alkaline solution separated from Na salt was shaken with AcOEt (50 ml×2), filtered, acidified with dil. H_2SO_4 and extracted with AcOEt (100 ml×3). The AcOEt extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to give 13 g of a dark brown paste, which was chromatographed through a column of 260 g of silica gel with $CHCl_3$ as eluent. The earlier fraction was concentrated to give 2.5 g of the second crop of V. Yield: 16.9%.

Methyl 2-Ethyl-5-methoxy-6-(2-methoxycarbonyl-6-methoxybenzoyl)-1-naphthoate (VIII)——A mixture of V (16 g), anhydrous K_2CO_3 (40 g), MeI (73 g) and dry Me_2CO (150 ml) was refluxed for 18 hr. After removing the solvent, the residual mass was extracted with $CHCl_3$ (50 ml×3). The $CHCl_3$ extract was filtered and evaporated to give 15 g of a brown paste, which was purified by column chromatography through alumina–benzene system to give 10 g (58.5%) of VIII as colorless crystals (MeOH–H_2O), mp 164°. *Anal.* Calcd. for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 69.16; H, 5.77. IR ν_{max}^{KBr} cm^{-1}: 1724, 1656 (C=O), 1621, 1600, 1587 (arom.).

2-Ethyl-5-methoxy-6-(2-carboxy-6-methoxybenzyl)-1-naphthoic Acid (IX)——A suspension of VIII (2.2 g), NaOH (20 g), Zn powder (20 g) (activated with ammoniacal $CuSO_4$) and H_2O (100 ml) was refluxed for 8 hr. Another Zn (10 g) together with NaOH (10 g) and H_2O (50 ml) was added and refluxing was continued for 9 hr. Further Zn (5 g) was added and refluxing was continued for 10 hr. After cooling, the alkaline solution was decanted, and the residual Zn mass was washed with hot H_2O (50 ml×2). The alkaline solution and the washings were combined and acidified with 20% H_2SO_4 to give colorless precipitates. Recrystallization from MeOH–H_2O (1:1) gave 1.7 g (85.5%) of IX as colorless crystals, mp 176°. *Anal.* Calcd. for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 69.97; H, 5.53.

2-Ethyl-5,7-dimethoxy-11-oxo-6,11-dihydro-1-naphthacenecarboxylic Acid (X)——A mixture of IX (1 g) and polyphosphoric acid (250 g) was heated with stirring at 100° for 10 min and poured onto 500 g of cracked ice. The brownish precipitates were collected, washed with H_2O, then with satd. $NaHCO_3$ and again with H_2O, and dried *in vacuo*. Three recrystallizations from Me_2CO gave 500 mg (52.3%) of pale yellow plates, mp 248°. *Anal.* Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.26; H, 5.36. IR ν_{max}^{KBr} cm^{-1}: 1729, 1649 (C=O), 1616, 1605, 1587, 1570 (shoulder) (arom.).

Methyl 2-Ethyl-5,7-dimethoxy-11-oxo-6,11-dihydro-1-naphthacenecarboxylate (XI)——To a suspension of X (500 mg) in ether (50 ml) was added dropwise a solution of CH_2N_2 in ether under ice-cooling until yellow color persisted after 1 hr. The solvent was removed under a reduced pressure at room temperature to give 510 mg of crystals. Three recrystallizations from benzene-cyclohexane (2:1) gave 400 mg (77.1%) of XI as colorless needles, mp 192—194°. *Anal.* Calcd. for $C_{24}H_{22}O_5 \cdot \frac{1}{3}C_6H_{12}$ (cyclohexane): C, 74.62; H, 6.26. Found: C, 74.62; H, 6.24. IR ν_{max}^{KBr} cm^{-1}: 1720, 1666 (C=O), 1621, 1605, 1592, 1570 (arom.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1721, 1661 (C=O), 1616 (shoulder), 1603, 1590, 1570 (shoulder) (arom.). UV $\lambda_{max}^{95\%\ EtOH}$ $m\mu$ (ε): 230 (35400), 259 (28700), 308 (9390), 320 (9920), 350 (7260). NMR ($CHCl_3$): 5.7 τ (2H, singlet, 6-CH_2-).

Methyl 2-Ethyl-5,7-dimethoxy-6,11-dioxo-6,11-dihydro-1-naphthacenecarboxylate (XII)——To an ice-cooled solution of XI (250 mg) in AcOH[10] (10 ml) was added a solution of CrO_3 (200 mg, 2.5 mole equiv.) in AcOH[10] (4 ml), and the mixture was allowed to stand at room temperature for 1 hr. The dark brown mixture was diluted with 100 ml of $CHCl_3$, washed three times with H_2O, twice with saturated. $NaHCO_3$ and then with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a yellowish brown solid, which was subjected to column chromatography on alumina employing $CHCl_3$ as eluent. The first fraction gave 120 mg (46.4%) of XII as bright yellow crystals, mp 197°, after recrystallization from Me_2CO. *Anal.* Calcd. for $C_{24}H_{20}O_6$: C, 71.28; H, 4.99. Found: C, 71.41; H, 4.87. IR ν_{max}^{KBr} cm^{-1}: 1727, 1669 (C=O), 1608, 1582 (arom.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724, 1672 (C=O), 1610, 1590 (arom.). UV $\lambda_{max}^{95\%\ EtOH}$ $m\mu$ (ε): 240 (69900), 290 (31800), 299 (34100), 410 (12700).

Methyl 2-Ethyl-5,7-dihydroxy-6,11-dioxo-6,11-dihydro-1-naphthacenecarboxylate (II) (Bisanhydroaklavinone)——To a cold solution of XII (50 mg) in dry CH_2Cl_2 (20 ml) was added a mixture of BBr_3 (1.04 g, 11 equiv.) and dry CH_2Cl_2 (10 ml) in one portion at −60°, and the mixture was allowed to warm up to room temperature and stand for 1 hr. The resulting deep blue mixture was poured onto cracked ice and extracted with AcOEt (100 ml×3). The extract was washed with satd. $NaHCO_3$ (30 ml×3) and then H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residual bright orange solid was chromatographed on silica gel by employing $CHCl_3$ as eluent to give 30 mg (64.5%) of II as orange needles, mp 234—236°. *Anal.* Calcd. for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29. Found: C, 70.40; H, 4.22. IR ν_{max}^{KBr} cm^{-1}: 1724, 1667 (C=O), 1616, 1600, 1572 (arom.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727, 1672 (C=O), 1618, 1603, 1572 (arom.). UV $\lambda_{max}^{n\text{-hexane}}$ $m\mu$ (ε): 242 (45500), 255 (43000), 262 (48000), 279 (18500), 290 (19150), 445 (18800), 462 (15300), 474 (15700). (Bisanhydroaklavinone[3]): mp 236°, IR ν_{max}^{Nujol} cm^{-1}: 1740, 1678, 1627, 1602, 1579. UV $\lambda_{max}^{n\text{-hexane}}$ $m\mu$ (ε): 242 (45100), 262 (47400), 279 (19300), 290 (19600), 440 (18900), 453 (16500), 462 (14600), 474 (15800)).

The IR spectrum of II was exactly superimposed on that of natural bisanhydroaklavinone, and the ultraviolet and visible spectra and the melting point were also in good agreement with those of natural source.

Acknowledgement The authors are grateful to Professor W.D. Ollis for providing the infrared, visible and ultraviolet spectra of bisanhydroaklavinone.

10) Acetic acid was freshly distilled over potassium permanganate.