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## 26. Zen-ichi Horii, Koichi Morikawa, Masaori Naruse, and Yasumitsu Tamura : Studies on Oxytetracycline and Related Compounds. XVIII.[1] Syntheses of 1-Hydroxy-3,10-dimethylanthrone and 6-Hydroxy-12-methyl-5(12*H*)-naphthacenone.

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In continuation of the works[1,2] on terrarubein (I), synthetic methods of the partial structure, the B and C rings, have been investigated. The present paper describes the transformation from 1-hydroxy-3-methylanthraquinone (II) to 1-hydroxy-3,10-dimethylanthrone (VI) and from 6-hydroxy-5,12-naphthacenequinone (IX) to 6-hydroxy-12-methyl-5(12*H*)-naphthacenone (IX), as a model experiment for this purpose.

It was known that the Grignard reagent reacted with either one or both of the carbonyl groups of anthraquinone to $\rangle$C(OH)R grouping.[3] Recently, Awad, *et al.*[4] reported that the Grignard reagent added preferentially to the carbonyl group of anthraquinone monoanil under ordinary conditions and the product thus obtained from anthraquinone monoanil and phenylmagnesium bromide was converted to 10-phenylanthrone by successive alcoholysis and later reduction. After the Grignard reaction of the quinone II was carried out with an excess of methylmagnesium iodide under ice-cooling for two hours in ethereal solution, the product was purified to 1,10-dihydroxy-3,10-dimethylanthrone (III), and following by the reduction with a mixture of hydroiodic acid and glacial acetic acid at 100° for half an hour gave (VI). On the other hand, treatment of III with a boiling mixture of sodium acetate and acetic anhydride in the presence of zinc dust, yielded 1,9-diacetoxy-3,10-dimethylanthracene (V). Followed by the hydrolysis with hydrochloric acid giving VI, which was identified with a sample of VI prepared above. The Grignard reaction of the naphthacenequinone IX with methylmagnesium iodide in tetrahydrofuran solution[*2] at refluxing temperature afforded 12-methyl-6,12-dihydroxy-5(12*H*)-naphthacenone (X) by chromatographic purification, being reduced with hydriodic acid to XI. When the methyl ether XII to IX was subjected to the Grignard reaction with methylmagnesium iodide, 6-methoxy-5,12-dimethyl-5,12-dihydro-5,12-naphthacenediol (XIII) was main product.

It was known that anthrone reacts with methyl iodide in potassium hydroxyide solution yielding 9-methoxy-10-methylanthracene,[5] and that the condensation with formaline in the presence of piperidine yielded 10-methyleneanthrone, being reduced to 10-methylanthrone.[6] If these reactions were applicable to 1-hydroxy-3-methylanthrone (VIII),[7] they would offer alternative routes for the preparation of VI. However, the reaction of VIII with formaline and methyl iodide under the same conditions as reported gave only resinous material.

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[*2] Since the compound IX is sparingly soluble in ether, xylene, tetrahydrofuran or dioxane was employed as a convenient solvent in the reaction. In only the case of employing tetrahydro- furan, compound X was isolated.

1) Part XVII. This Bulletin, **10**, 946 (1962).
2) Part XVI. *Ibid.*, **10**, 1013 (1962).
3) G. A. Guyot and C. Steahling : Bull. soc. chim. France, [3] **33**, 1104, 1144 (1905); Chem. Zentr., **1906**, I, 45, 47.
4) W. I. Awad, A. K. Fateen and M. A. Zayed : J. Org. Chem., **25**, 359 (1960).
5) K. H. Meyer and H. Schlösser : Ann., **420**, 126 (1920). H. Heymann and L. Trowbridge : J. Am. Chem. Soc., **72**, 85 (1950).
6) E. B. Barnett and M. A. Matthews : Ber., **59**, 767 (1926).
7) A. Steyermark and J. H. Gardner : J. Am. Chem. Soc., **52**, 4891 (1930).

The constitutions of III, VI, X, and XI were determined by their infrared spectra, showing carbonyl stretching absorption band at considerably lower frequency (below 1634 cm$^{-1}$) as shown in Table I and those of VI and XI have no hydroxyl stretching frequency at the region over 3000 cm$^{-1}$. These facts would indicate that all these compounds have the structures assigned, in which the carbonyl group chelates with hydroxyl group in *peri*-position.

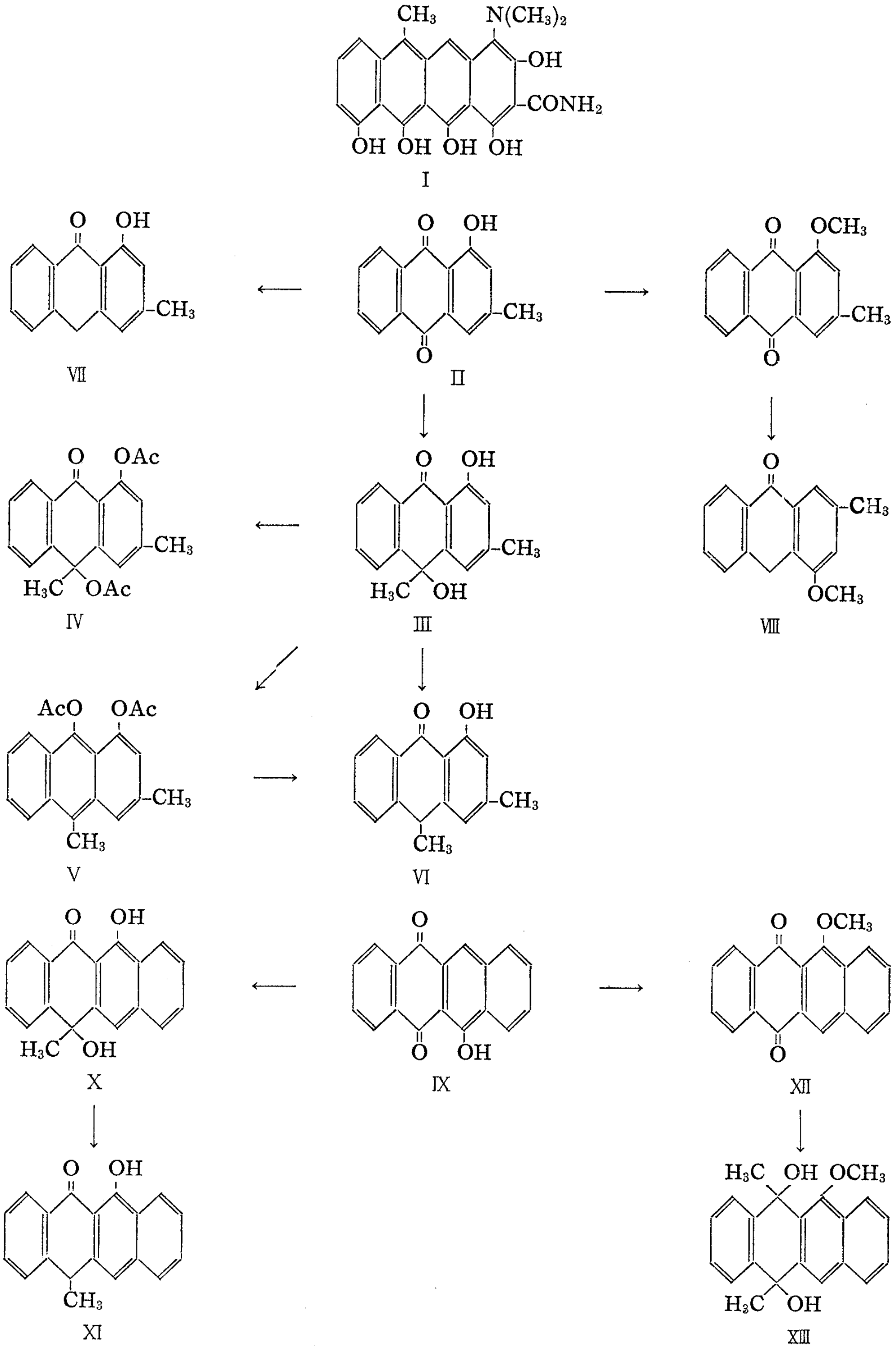
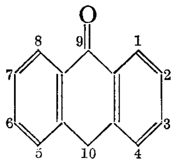
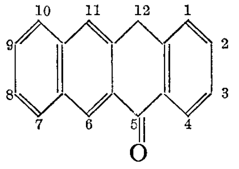


Chart 1.

TABLE I. Carbonyl Absorption ($cm^{-1}$) in Infrared Spectrum



| | | |
|---|---|---|
| Anthrone[d] | | 1654 |
| 2,4-Dimethoxy-[b] | 1656[e] | 1658[f] |
| Barbaloin heptamethyl ether[d] | | 1680 |
| 4-Hydroxy-[a] | | 1640[e] |
| 4-Methoxy-2-methyl- (VIII) | | 1655[e] |
| 1,10-Diacetoxy-3,10-dimethyl- (IV) | | 1661[f] |
| Aloe-emodin-[d] (1,8-Dihydroxy-3-hydroxymethyl-) | | 1631 |
| Barbaloin[d] | | 1630 |
| 1,8-Dihydroxy-[d] | | 1636 |
| 1-Hydroxy-[a] | | 1634[e] |
| 1,10-Dihydroxy-3,10-dimethyl- (III) | | 1631[f] |
| 1-Hydorxy-3,10-dimethyl- (VI) | | 1634[f] |
| 1-Hydroxy-3-methyl-[a] (VII) | | 1630[f] |



| | |
|---|---|
| 5(12*H*)Naphthacenone | |
| 1,3,11-Trimethoxy-[c] | 1653[e] |
| 11-Methoxy-[b] | 1653[e] |
| 6-Hydroxy-12-methyl- (XI) | 1625[e] |
| 6,12-Dihydroxy-12-methyl- (X) | 1622[e] |

*a*) Prepared by the method of Steyermark. See reference 7).

*b*) See reference 1). *c*) See reference 2).

*d*) J.E. Hay and L.J. Haynes: J. Chem. Soc., **1956**, 3141. No description about the solvent employed for measurement.

*e*) Nujol. *f*) in $CHCl_3$.

## Experimental

**1-Hydroxy-3-methylanthraquinone (II)**——Prepared by the method of Eder[8] from 2-(2-hydorxy-4-methylbenzoyl)benzoic acid, which was obtainable by the method of Ullmann,[9] m.p. 178°.

**1,10-Dihydroxy-3,10-dimethylanthrone (III)**——To an ice-cooled solution of 4 g. (16.8 mmole) of II in 150 cc. of benzene was added dropwise an $Et_2O$ solution of MeMgI which was prepared from 11.9 g. (84 mmole) of MeI, 2.04 g. (84 mmole) of Mg and 20 cc. of $Et_2O$. The solution was stirred for 2 hr. under ice-cooling and poured into $NH_4Cl$ solution. The aqueous layer was extracted with $Et_2O$, and the combined extracts were washed with $H_2O$, dried and concentrated. The residual yellow crystals were chromatographed on silica-gel with benzene. The first band of crystalline material 400 mg. eluted was a recovery of the starting material II and the second band eluted (2.5 g., 57%) yielded, on crystallization from benzene-petr. benzin, light yellow plates III, m.p. 151~152°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $cm^{-1}$: 1631 (C=O), 3436, 3546 (OH). *Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.95; H, 5.53.

**1,10-Diacetoxy-3,10-dimethylanthrone (IV)**——To a solution of 100 mg. (0.39 mmole) of III in 1.5 cc. of pyridine was added 1.5 cc of $Ac_2O$ and the mixture was refluxed gently for 1 hr. After cooling, the reaction mixture was dilutedwith ice water and extracted with $Et_2O$, which was washed with $H_2O$, dried and concentrated. The residue was recrystallized from EtOH giving 100 mg. (71%) of colorless prisms, m.p. 159.5~161°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $cm^{-1}$: 1745, 1701 (AcO-), 1661 (C=O). *Anal.* Calcd. for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.08; H, 5.56.

**1,9-Diacetoxy-3,10-dimethylanthracene (V)**——A mixture of 200 mg. (0.79 mmole) of III, 40 cc. of $Ac_2O$, and 200 mg. of AcONa was refluxed for 1 hr. with 1 g. of Zn powder. The reaction mixture was filtered and the residual Zn powder was washed with hot AcOH. The filtrate and washings were combined and diluted ice water. The precipitate was filtered and recrystallized from glacial AcOH giving 160 mg. (63%) of yellow needles, m.p. 224~226°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$: 1761 $cm^{-1}$ (AcO-). *Anal.* Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.73; H, 5.57.

**1-Hydroxy-3,10-dimethylanthrone (VI)**——a) Reduction of III with HI: A solution of 200 mg. of III and 1 cc. of 57% HI in 3 cc. of glacial AcOH was maintained at 90~100° for 30 min. After cooling, the reaction mixture was poured into $NaHSO_2$ solution and extracted with $Et_2O$, which was washed with $NaHCO_3$ solution and then $H_2O$, dried and concentrated. The residual light yellow crystals were purified by chromatography on silica-gel, eluted with benzene and recrystallized from petr. benzin to give 150 mg. (80%) of VI, m.p. 71~72°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $cm^{-1}$: 1634 (C=O). *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.58; H, 5.81.

b) Hydrolysis of V: A solution of 200 mg. (0.62 mmole) of V, 3 cc. of glacial AcOH and 5 drops each of conc. HCl and $H_2O$ was refluxed for 40 min. The reaction mixture was decomposed with ice water and extracted with $Et_2O$, which was washed with $NaHCO_3$ solution and $H_2O$, dried and concentrated. The residue was recrystallized from petr. benzin to give 105 mg. (73%) of crystals, m.p. 71~72°,

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[8] R. Eder and O. Manoukian: Helv. Chim. Acta, **9**, 53 (1926).

[9] F. Ullmann and W. Schmidt: Ber., **52**, 2098 (1919).

which was identical with a sample of VI prepared in a) by mixed melting point determination and comparison of their IR spectra. *Anal.* Calcd. for $C_{16}H_{14}O_2$ : C, 80.64; H, 5.92. Found : C, 80.64; H, 5.96.

**1-Hydroxy-3-methylanthrone (VII)**——Prepared[7] from II by the method of Steyermark, m.p. 159~161°. IR $\nu_{max}^{CHCl_3}$ : 1630 $cm^{-1}$(C=O).

**4-Methoxy-2-methylanthrone (VIII)**——A mixture of 2 g. (8.4 mmole) of II, 10 g. of anhyd. $K_2CO_3$, 10 g. of $CH_3I$ and 100 cc. of $Me_2CO$ was refluxed for 24 hr. The reaction mixture was filtered while hot and cooled, depositing yellow crystals. Recrystallization from glacial AcOH gave 1.5 g. (74%) of 1-methoxy-3-methylanthraquinone, m.p. 187~188° (Lit.[10] 187~188°).

To a solution of 500 mg. of 1-methoxy-3-methylanthraquinone in 100 cc. of MeOH was added a solution of 3 g. NaOH, 5.5 g. of $Na_2S_2O_4$, 20 cc. of MeOH and 80 cc. of $H_2O$ and the mixture was refluxed for 6 hr. After cooling, the mixture was poured into $H_2O$ and extracted with $Et_2O$, which was washed with $H_2O$, dried and evaporated. The residue was recrystallized from MeOH to give 235 mg. (48%) of VIII as yellow needles, m.p. 149~151°. An analytical sample, m.p. 151~152°, was prepared by further recrystallizations from the same solvent. *Anal.* Calcd. for $C_{16}H_{14}O_2$ : C, 80.64; H, 5.92. Found : C, 80.52; H, 5.85. IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1655 (C=O).

**6-Hydroxy-5, 12-naphthacenequinone (IX)**——Prepared[11] by the cyclization of *o*-(1-hydroxy-2-naphthoyl)benzoic acid[12] with conc. $H_2SO_4$ in the presence of $H_3BO_3$, m.p. 303~304°.

**12-Methyl-6, 12-dihydroxy-5(12*H*)-naphthacenone (X)**——To a solution of 1 g. (3.6 mmole) of 6-hydroxy-5, 12-naphthacenequinone (IX)[1] in 250 cc. of tetrahydrofuran was added dropwise an $Et_2O$ solution of MeMgI prepared from 3 g. (21.1 mmole) of $CH_3I$, 500 mg. (21.0 mmole) of Mg and 5 cc. of $Et_2O$. The reaction mixture was stirred for 3 hr. under refluxing, cooled and poured into $NH_4Cl$ solution. The aqueous layer was extracted with $Et_2O$, which was washed with $H_2O$, dried and concentrated. The brownish-yellow residue was dissolved in 80 cc. of cold $Et_2O$ and deep red insoluble material was filtered off. The almost all insoluble substances (142 mg.) were found the starting material IX by its IR spectrum. The $Et_2O$ filtrate was evaporated and the residue was again dissolved in 25 cc. of warm $Et_2O$ giving further 93 mg. of the insoluble material. The $Et_2O$ solution thus obtained was concentrated and the orange colored residue was chromatographed over 25 g. of silica-gel. First elution with benzene-petr. benzin mixture (1:9) (2550 cc.) gave a small amount of the starting material IX and second elution with benzene-petr. benzin mixture (3:7) (450 cc.) gave 280 mg. (27%) of X as orange colored crystals, m.p. 168~170°. An analytical sample was prepared by recrystallization from benzene, m.p. 171~172°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 3484 (OH), 1622 (C=O). *Anal.* Calcd. for $C_{19}H_{14}O_3$ : C, 78.60; H, 4.85. Found : C, 78.82; H, 4.85.

**6-Hydroxy-12-methyl-5(12*H*)-naphthacenone (XI)**——To an ice-cooled solution of 130 mg. of X in 12 cc. of glacial AcOH was added a mixture of 1.3 g. of 57% HI and 3 cc. of glacial AcOH and the mixture was refluxed for 1 hr. under $N_2$ atmosphere. From the mixture, 6.5 cc. of AcOH was removed and the residue was poured into ice-$NaHSO_3$ solution. The brownish-yellow precipitates were collected, washed with $H_2O$, dried and recrystallized several times from benzene giving 90 mg. (73%) of XI, m.p. 235~236° (decomp.). IR $\nu_{max}^{Nujol}$ : 1625 $cm^{-1}$(C=O). *Anal.* Calcd. for $C_{19}H_{14}O_2$ : C, 83.20; H, 5.15. Found: C, 82.93; H, 5.00.

**6-Methoxy-5, 12-naphthacenequinone (XII)**——Prepared by methylation of IX[11] with $Me_2SO_4$ and NaOH solution. m.p. 210~212°.

**Reaction of 6-Methoxy-5, 12-naphthacenequinone (XII) with MeMgI**——To an ice-cooled solution of 500 mg. (1.74 mmole) of XII in tetrahydrofuran was added $Et_2O$ solution of MeMgI prepared from 2.47 g. (17.4 mmole) of MeI, 423 mg. (17.4 mmole) of Mg and $Et_2O$. The mixture was stirred for 2 hr. and to this was added $NH_4Cl$ solution. The whole mixture was extracted with $Et_2O$, which was washed with $H_2O$, dried and concentrated. The residue was purified through silica-gel column. Elution with $Et_2O$ gave 100 mg. of colorless needles of 6-methoxy-5,12-dimethyl-5,12-dihydro-5,12-napythacenediol (XIII), m.p. 210~211°. IR $\nu_{max}^{Nujol}$ 3367 $cm^{-1}$(OH). *Anal.* Calcd. for $C_{21}H_{20}O_3$ : C, 78.72; H, 6.29. Found : C, 78.79; H, 6.11.

## Summary

The Grignard reaction of 1-hydroxy-3-methylanthraquinone (II) with methylmagnesium iodide yielded 1,10-dihydroxy-3,10-dimethylanthrone (III), which was converted to 3,10-dimethyl-1-hydroxyanthrone (VI) by reduction with hydriodic acid. Compound VI was also obtained by hydrolysis with hydrochloric acid of 1,9-diacetoxy-3,10-dimethylanthracene (V), which was prepared by reductive acetylation of III with zinc dust, sodium acetate and acetic anhydride. The method was also found to be applicable to 6-hydroxy-5,12-naphthacenequinone (IX), thus giving 6-hydroxy-12-methyl-5(12*H*)-naphthacenone (XI).

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10) S. Shibata : Pharm. Bull., **3**, 156 (1955).
11) G. Wolf : J. Am. Chem. Soc., **75**, 2673 (1953).
12) C. Deichler and C. Weizmann : Ber., **36**, 559 (1903).