Synthesis of 5,8-Dihydroxy-2-methoxy-1,4-naphthoquinone Derivatives. A Major Naphthoquinone Moiety of Some of Naphthoquinone Antibiotics[1)]

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6-Formyl- and 6-hydroxymethyl-5,8-dihydroxy-2-methoxy-1,4-naphthoquinones were, respectively, prepared from 2-formyl- and 2-hydroxymethyl-1,4,5,6,8-pentamethoxynaphthalenes which were synthesized as key intermediates of the new antibiotics containing 2-methoxynaphthazarin structure.

Fusarubin (**1**),[2)] Erythrostominone (**2**),[2)] Purpuromycin (**3**),[3)] and Fredericamycin A (**4**)[4)] are new antibiotics of naphthoquinone series, and commonly have a 2-methoxynaphthazarin moiety, that is 5,8-dihydroxy-2-methoxy-1,4-naphthoquinone part (Fig. 1). Although there have been some reports[5)] concerning the spiro part construction of **4**, no literature was found regarding the naphthoquinone part.

Recently, we have found an efficient methodology for this 2-methoxynaphthazarin system such as 6-formyl- and 6-hydroxymethyl-5,8-dihydroxy-2-methoxy-1,4-naphthoquinones (**10**) and (**13**) from 2-formyl- and 2-hydroxymethyl-1,4,5,6,8-pentamethoxynaphthalenes (**8**) and (**11**). These compounds have been synthesized in our laboratory as key intermediates for the antibiotics described above. The results prompt us to report at this time.

Results and Discussion

Demethylation of 2-formyl-1,4,5,8-tetramethoxynaphthalene (**5**)[6)] with ceric(IV) ammonium nitrate (CAN is used as the abbreviation hereafter) gave 6-formyl-5,8-dimethoxy-1,4-naphthoquinone (**6**) in 85% yield. Only two methoxyl groups of 5- and 8-positions of the original **5** had been cleaved by the oxidation. A treatment of **6** with acetic anhydride in the presence of a catalytic amount of sulfuric acid at room temperature gave 1,2,4-triacetoxy-6-diacetoxymethyl-5,8-dimethoxynaphthalene (**7**) in 98% yield. As shown later in this text, it will be proved that one acetoxyl substituent introduced newly among the five acetoxyl groups, occupied the 2-position in **7**; this conclusion is due to an NMR-structural study of **13** (see later). An alkaline hydrolysis of **7**, and methylation with dimethyl sulfate gave **8** in 67% yield. Demethylation of **8** with CAN afforded 6-formyl-2,5,8-trimethoxy-1,4-naphthoquinone (**9**), where only 5- and 8-positional methoxyl groups were cleaved similarly to the demethylation of **5**. A further demethylation of **9** with aluminum chloride at room temperature gave **10**, and the 2-positional methoxyl group remained unchanged (Scheme 1).

Another target **13** was obtained as follows (Scheme 2). A reduction of the aldehyde **8** with lithium aluminum hydride easily gave the correspoding alcohol **11**. Demethylation of **11** with CAN afforded 6-hydroxymethyl-2,5,8-trimethoxy-1,4-naphthoquinone (**12**), which gave **13** (43%) and 5-hydroxy-6-hydroxymethyl-2,8-dimethoxy-1,4-naphthoquinone (**14**) (38%) by further demethylation with aluminum chloride at room temperature. A prolonged reaction time (20 h), however, resulted in the formation of **13** only in 20% yield, with an unidentified product.

The structure of **13** was established on the basis of an NMR-study,[7)] of 5,8-dihydroxy-2-methoxy-1,4-naphthoquinone (**15**). The C_8-OH and C_5-OH protons in **15** absorbed at δ 12.17 and 12.63, respectiviely.[7)] It is well-

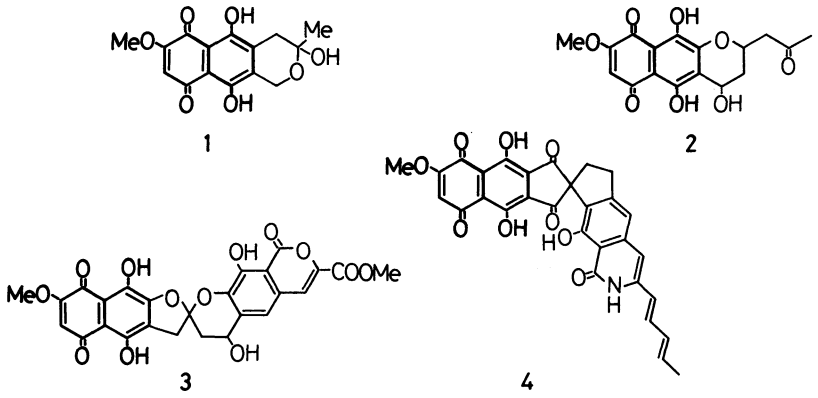
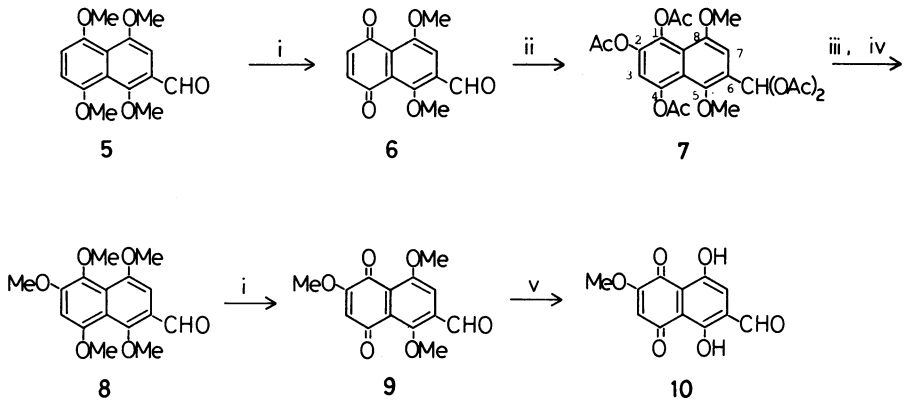
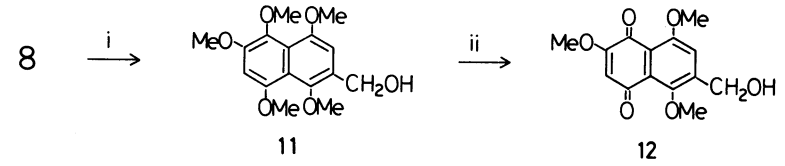


Fig. 1.



Scheme. 1. i: $(NH_4)_2Ce(NO_3)_6$, H_2O, CH_3CN; ii: Ac_2O, H_2SO_4; iii: OH^-, CH_3OH; iv: OH^-, $(CH_3)_2SO_4$; v: $AlCl_3$, CH_2Cl_2.



Scheme 2. i: $LiAlH_4$, THF; ii: $(NH_4)_2Ce(NO_3)_6$, H_2O, CH_3CN, $CHCl_3$; iii: $AlCl_3$, CH_2Cl_2.

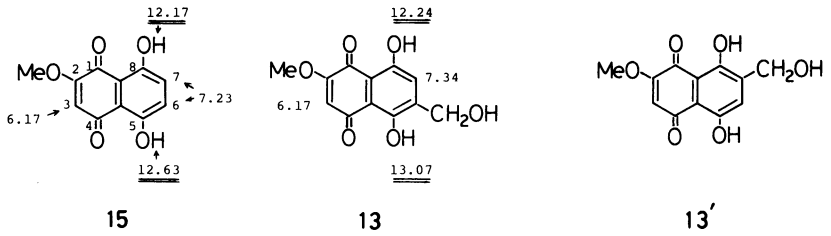


Fig. 2.

known that if **15** has a substituent at either the 6- or 7-position, the chemical shift of the OH proton adjacent to the substituent generally moves in an appreciable extent.[7] In our product **13**, the chemical shift of the C_8-OH proton almost remained unchanged at δ 12.24, whereas that of C_5-OH was found at δ 13.07. As the C_5-OH in our product **13** was observed more downfield than that of **15**, the hydroxymethyl substituent in **13** must be at the 6-position. Therefore, it was concluded that the structure of our product should not be **13'**, but **13**. Then, it could be proved that one of the acetoxyl groups newly introduced by the conversion of **6** to **7**, occupied the 2-position of **7**.

If an aromatic ring has either a formyl or a hydroxymethyl substituent, an ortho-lithiation of the ring is generally possible by the use of butyllithium.[8] Here, the obtained products **8** and **11** have such possibilities to receive new side-chain introductions at their 3-positions; we will be able to apply this to intermediates for syntheses of naphthoquinone antibiotics.

Experimental

^1H NMR spectra were taken on a JEOL JNM-FX60 in $CDCl_3$ and showed in δ values. Mass spectra were obtained with a JEOL DX-300. IR spectra were recorded on a Hitachi 260-30. Column chromatography was carried out on silica gel (Wakogel C-200) with chloroform as an eluent. Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected.

6-Formyl-5,8-dimethoxy-1,4-naphthoquinone (6). A solution of CAN (26 g, 47.7 mmol) in water (60 ml) was added to a solution of the aldehyde **5** (5.15 g, 18.7 mmol) in acetonitrile (100 ml) at room temperature, stirred for 30 min, then diluted with water (300 ml). The precipitate was filtered,

washed with water, dried, and gave 3.4 g (74%) of **6** as yellow crystals, mp 175—177 °C. The filtrate was extracted with chloroform. The chloroform solution was washed with brine, dried, and evaporated. Chromatographic purification of the crude product gave 0.51 g (11%) of a sample of **6**. Recrystallization from ligroine-benzene gave an analytical sample, mp 177—178 °C. IR (KBr) 1695 (aldehyde C=O), 1665 (quinone C=O), 1055, and 1020 cm^{-1}; MS m/z 246 (M^+), 232, 216, 200, and 189; ^1H NMR δ=4.03 (s, 6H, OCH_3), 6.87 (s, 2H, quinonoid ring H), and 7.77 (s, 1H, benzenoid ring H). Found: C, 63.27; H, 4.06%. Calcd for $C_{13}H_{10}O_5$: C, 63.72; H, 4.09%.

1,2,4-Triacetoxy-6-diacetoxymethyl-5,8-dimethoxynaphthalene (7). A mixture of **6** (8.2 g, 33.4 mmol) in acetic anhydride (50 ml) and concd sulfuric acid (0.5 ml) was allowed to stand at room temperature for 10 d, then poured into ice water and extracted with chloroform. The usual work-up and chromatography gave 16.2 g (98%) of a sample of **7**. Recrystallization from hexane-ethanol gave an analytical sample, mp 174—175 °C. IR (KBr) 1760 (C=O), 1610, 1365, 1200, and 1035 cm^{-1}; MS m/z 492 (M^+), 450, 408, 366, and 264; ^1H NMR δ=2.11 (s, 6H, CH_3), 2.32 (s, 3H, CH_3), 2.35 (s, 6H, CH_3), 3.86, 3.93 (each s, 3H, OCH_3), 6.96, 7.08 (each s, 1H, ArH), and 8.15 (s, 1H, CH). Found: C, 56.09; H, 4.94%. Calcd for $C_{23}H_{24}O_{12}$: C, 56.10; H, 4.91%.

2-Formyl-1,4,5,6,8-pentamethoxynaphthalene (8). Sodium hydroxide (12 g, 0.3 mol) dissolved in water (50 ml) was added dropwise to a suspension of **7** (9.93 g, 20 mmol) in methanol (50 ml) under a nitrogen atmosphere and stirred for 1 h. To this was added dimethyl sulfate (76 g, 0.6 mol) and sodium hydroxide (12 g, 0.3 mol) in water (50 ml) alternately and stirred at 40 °C for 5 h. After concentration, the system was extracted with chloroform, worked up as usual, and chromatographed to give 4.14 g (67%) of a sample of **8**. Recrystallization from hexane-ethanol gave yellow crystals, mp 153.5—155.5 °C. IR (KBr) 1660 (C=O), 1595, 1360, 1070, and 1045 cm^{-1}; MS m/z 306 (M^+), 291, 276, 263, and 258; ^1H NMR δ=3.81, 3.90, 3.98, 4.01, 4.03 (each s, 3H, OCH_3), 6.78, 7.13 (each s, 1H, ArH), and 10.47 (s, 1H, CHO). Found: C, 62.58; H, 5.92%. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92%.

6-Formyl-2,5,8-trimethoxy-1,4-naphthoquinone (9). A solution of CAN (4.0 g, 7.35 mmol) in water (40 ml) was added dropwise to a solution of **8** (0.9 g, 2.94 mmol) in acetonitrile (50 ml), stirred at room temperature for 30 min, then diluted with water and extracted with chloroform. The usual work-up and chromatography gave 0.72 g (89%) of a sample of **9**. Recrystallization from ligroine gave orange crystals, mp 239—241 °C. IR (KBr) 1680 (aldehyde C=O), 1650, 1630 (each quinone C=O), 1585, 1205, 1055, and 1020 cm^{-1}; MS m/z 276 (M^+) and 261; ^1H NMR δ=3.88, 3.99, 4.02 (each s, 3H, OCH_3), 6.08 (s, 1H, quinonoid ring H), 7.71 (s, 1H, benzenoid ring H), and 10.50 (s, 1H, CHO). Found: C, 60.83; H, 4.45%. Calcd for $C_{14}H_{14}O_6$: C, 60.87; H, 4.38%.

6-Formyl-5,8-dihydroxy-2-methoxy-1,4-naphthoquinone (10). Anhydrous aluminum chloride (0.48 g, 3.6 mmol) was added to a solution of **9** (0.1 g, 0.36 mmol) in dichloromethane (30 ml), stirred at room temperature for 20 h, decomposed by an addition of 5% aqueous oxalic acid (100 ml), and extracted with chloroform. After the usual work-up, the crude product was chromatographed to give 30 mg (33%) of a sample of **10**, mp 243—244 °C (decomp). IR (KBr) 1690 (aldehyde C=O), 1615 (quinone C=O), 1590, 1560, 1430, 1195, and 1030 cm^{-1}; MS m/z 248 (M^+), 220, and 202; ^1H NMR δ=3.98 (s, 3H, OCH_3), 6.25 (s, 1H, quinonoid ring H), 7.75 (s, 1H, benzenoid ring H), 10.55 (s, 1H, CHO), 11.76, and 13.11 (each s, 1H, ArOH). Found: C, 57.70; H, 3.86%. Calcd for $C_{12}H_8O_8$: C, 58.07; H, 3.25%.

2-Hydroxymethyl-1,4,5,6,8-pentamethoxynaphthalene (11). A solution of **8** (0.26 g, 0.86 mmol) in tetrahydrofuran (15 ml) was treated with lithium aluminum hydride (65 mg, 1.7 mmol) under ice cooling, stirred at room temperature for 3 h, then decomposed by an addition of dil hydrochloric acid, and extracted with chloroform. The usual work-up and chromatography gave 0.21 g (78%) of a sample of **11**. Recrystallization from ligroine-benzene gave an analytical sample, mp 138—139 °C. IR (KBr) 3480 (sharp, OH), 1600, 1460, 1370, 1070, and 1050 cm^{-1}; MS m/z 308 (M^+), 293 (M^+-CH_3), 265, and 71; ^1H NMR δ=2.33 (s, 1H, OH), 3.77, 3.80, 3.93 (each s, 3H, OCH_3), 3.98 (s, 6H, OCH_3), 4.81 (s, 2H, CH_2), 6.74, and 6.86 (each s, 1H, ArH). Found: C, 62.57; H, 6.59%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%.

6-Hydroxymethyl-2,5,8-trimethoxy-1,4-naphthoquinone (12). Treatment of **11** (0.57 g, 1.85 mmol) in a mixture of acetonitrile (20 ml) and chloroform (2 ml) with CAN (2.54 g, 4.63 mmol) in water (8 ml) gave a crude product. Chromatography of the crude product gave 0.35 g (68 %) of a sample of **12**. Recrystallization from ethanol gave orange crystals, mp 216.5—217.5 °C. IR (KBr) 3490 (sharp, OH), 1645, 1620 (each C=O), 1585, 1205, 1065, and 1050 cm^{-1}; MS m/z 278 (M^+), 248, 234, and 217; ^1H NMR δ=2.21 (t, J=5.9 Hz, 1H, OH), 3.84 (s, 6H, OCH_3), 4.00 (s, 3H, OCH_3), 4.85 (d, J=5.9 Hz, 2H, CH_2), 6.01 (s, 1H, quinonoid ring H), and 7.43 (s, 1H, benzenoid ring H). Found: C, 60.31; H, 5.18%. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07%.

5,8-Dihydroxy-6-hydroxymethyl-2-methoxy-1,4-naphthoquinone (13) and 5-Hydroxy-6-hydroxymethyl-2,8-dimethoxy-1,4-naphthoquinone (14). The reaction of **12** (95 mg, 0.34 mmol) in dichloromethane (30 ml) with anhydrous aluminum chloride (0.46 g, 3.4 mmol) was carried out at room temperature for 2 h. Chromatography of the crude product gave two kinds of crystalline products. One was 37 mg (43%) of a sample of **13**. Recrystallization from ethanol gave reddish brown crystals, mp 218.5—219.5 °C. IR (KBr) 3540 (sharp, OH), 1615 (C=O), 1580, 1430, 1200, and 1080 cm^{-1}; MS m/z 250 (M^+), 232, and 221; ^1H NMR δ=2.20 (t, J=6.1 Hz, 1H, OH), 3.94 (s, 3H, OCH_3), 4.82 (d, J=6.1 Hz, 2H, CH_2), 6.17 (s, 1H, quinonoid ring H), 7.34 (s, 1H, benzenoid ring H), 12.24, and 13.07 (each s, 1H, ArOH). Found: C, 57.96; H, 4.45%. Calcd for $C_{12}H_{10}O_6$: C, 57.61; H, 4.03%.

The other was 34 mg (38%) of a sample of **14**. Recrystallization from ethanol gave reddish orange crystals, mp 222—224 °C. IR (KBr) 3570 (OH), 3470 (OH), 1630 (C=O), 1435, 1215, 1080, and 1050 cm^{-1}; MS m/z 264 (M^+), 246, and 203; ^1H NMR δ=2.31 (t, J=5.9 Hz, 1H, OH), 3.90, 4.00 (each s, 3H, OCH_3), 4.85 (d, J=5.9 Hz, 2H, CH_2), 6.05 (s, 1H, quinonoid ring H), 7.43 (s, 1H, benzenoid ring H), and 13.18 (s, 1H, ArOH). Found: C, 58.68; H, 4.61%. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58%.

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