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Monosubstituted Tetramethoxynaphthalenes[1)]

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As new intermediates for the syntheses of monosubstituted naphthazarins and anthracyclines, several tetramethoxynaphthalenes having a substituent such as CH_3, COOH, CN, Br, OAc, OH, and OMe groups were prepared from 1,4,5,8-tetramethoxynaphthalene and 2-formyl-1,4,5,8-tetramethoxynaphthalene.

We have already reported that 1,4,5,8-tetramethoxynaphthalene (**1**) could be converted to 2-formyl-1,4,5,8-tetramethoxynaphthalene (**2**) in almost quantitative yield; from this, (±)shikonin was first prepared.[2)] Generally, tetramethoxynaphthalens could be easily demethylated by our methods to give the corresponding naphthazarin compounds[3)] (Scheme 1). The tetramethoxynaphthalene **1** was used as an intermediate in the synthesis of nogalamycin,[4)] which belonged to anthracycline series antibiotics.

These results suggest to us the possibility that these monosubstituted tetramethoxynaphthalenes will become new intermediates for naphthoquinones and anthracyclines. Here, we consider the syntheses of monosubstituted tetramethoxynaphthalenes having CH_3, COOH, CN, Br, OAc, OH, or OMe as the substituent.

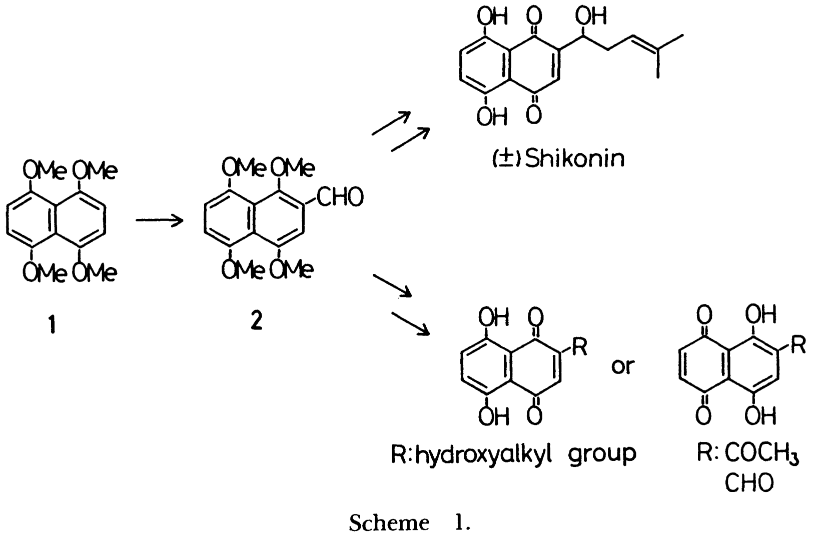
Results and Discussion

Reduction of the aldehyde **2** with $LiAlH_4$ gave 2-hydroxymethyl-1,4,5,8-tetramethoxynaphthalene (**3**),[3)] followed by hydrogenolysis in the presence of palladium carbon, 2-methyl-1,4,5,8-tetramethoxynaphthalene (**4**) resulted in 58% yield.

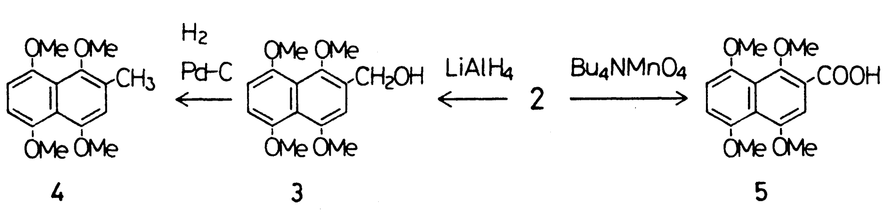
Although the oxidation of **2** with potassium permanganate gave a negative result, tetrabutylammonium permanganate[5)] was tried and our proposed 1,4,5,8-tetramethoxy-2-naphthoic acid (**5**) was obtained in 87% yield.

With chlorosulfonyl isocyanate[6)] in dichloromethane the tetramethoxynaphthalene **1** gave an *N*-chlorosulfonyl amide intermediate; subsequent treatment with DMF afforded 2-cyano-1,4,5,8-tetramethoxynaphthalene (**6**) in 71% yield (Scheme 3).

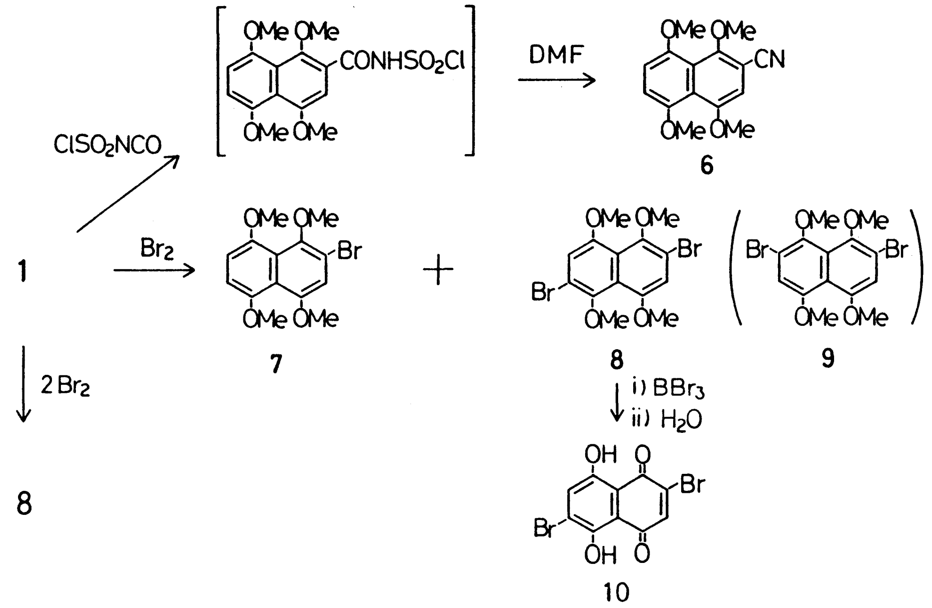
With an equimolar amount of bromine in chloroform, **1** gave 2-bromo-1,4,5,8-tetramethoxynaphthalene (**7**) (44% yield) and 2,6-dibromo-1,4,5,8-tetramethoxynaphthalene (**8**) (17%) at the same time. However, two molar equiv. of bromine wholly afforded the dibromide (**8**); the product yield was 87%. Since the structure of this dibromide was either 2,6-dibromide (**8**) or 2,7-



Scheme 1.



Scheme 2.



Scheme 3.

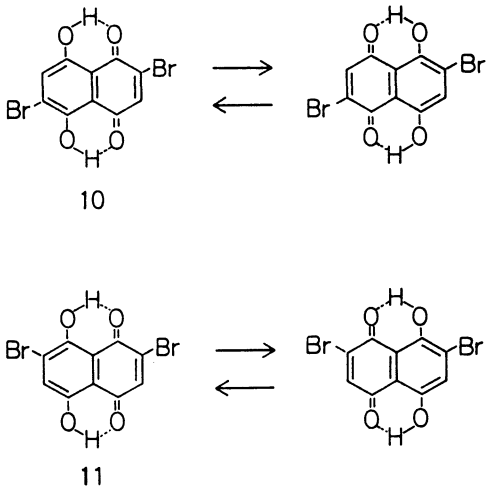
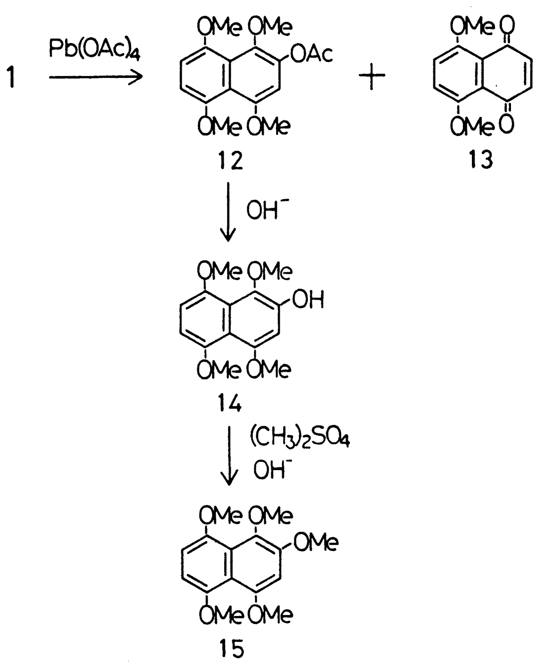


Chart 1.

dibromide (**9**), shown in Scheme 3, the dibromide was changed into a dibromonaphthazarin and identified as follows. Both the naphthazarin dibromides, **10** and **11** in Chart 1, are tautomers of each other. The dibromonaphthazarin which we obtained showed a sharp single peak in the ^{1}H NMR at δ 12.56 due to two equivalent hydroxyl groups. Since the naphthazarin was, therefore, **10**, the above dibromide was proved to be **8**. If the naphthazarin product was another **11**, its hydroxyl signal in ^{1}H NMR had to be separated into two peaks as like A in Chart 2.[7]

The treatment of **1** with lead tetraacetate in benzene gave 2-acetoxy-1,4,5,8-tetramethoxynaphthalene (**12**) (40% yield) and 5,8-dimethoxy-1,4-naphthoquinone (**13**) (46%). The structure of **13** was identical with that of the authentic sample[3] already obtained in our laboratory by the oxidative demethylation of **1** with cerium(IV) ammonium nitrate.



Scheme 4.

Alkali hydrolysis of **12** gave 1,4,5,8-tetramethoxy-2-naphthol (**14**) in 91% yield, and methylation with dimethyl sulfate afforded 1,2,4,5,8-pentamethoxynaphthalene (**15**) (Scheme 4).

Experimental

Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were taken on a JEOL JNM-60 in $CDCl_3$ using Me_4Si and $CDCl_3$ as internal standards, respectively. Mass spectra and IR spectra were obtained with a JEOL DX-300 spectrometer, and a Hitachi 260-30 spectrometer, respectively. Column chromatography was carried out on silica gel (Wakogel C-200) or alumina (Sumitomo, KCG-30) eluting with chloroform.

2-Methyl-1,4,5,8-tetramethoxynaphthalene (4). A mixture of 2-hydroxymethyl-1,4,5,8-tetramethoxynaphthalene (**3**)[3] (189 mg, 0.68 mmol) and palladium carbon (200 mg, Pd content 5%) in tetrahydrofuran (5 ml) and ethanol (30 ml) was stirred at 60 °C for 8 h under 50 kg cm^{-2} of hydrogen in an autoclave. After filtration and washing the residue with chloroform, evaporation of the combined filtrate gave a solid which was purified by alumina chromatography to give a sample of **4** (102 mg, 58%). Recrystallization from hexane gave an analytical sample, mp 95.5—96.5 °C. IR (KBr) 1600, 1355, 1260, and 1070 cm^{-1}; ^{1}H NMR δ=2.41 (s, 3H, CH_3), 3.73, 3.89 (each s, 3H, OCH_3), 3.92 (s, 6H, 2×OCH_3), 6.7 (s, 1H, ArH), and 6.78 (s, 2H, 2×ArH); MS, m/z 262 (M^+), 247 (M^+-CH_3), 204. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92%. Found: C, 68.30; H, 6.58%.

1,4,5,8-Tetramethoxy-2-naphthoic Acid (5). Tetrabutylammonium permanganate[5] (360 mg, 1 mmol) was added to a solution of 2-formyl-1,4,5,8-tetramethoxynaphthalene[2] (**2**) (138 mg, 0.5 mmol) in pyridine (3 ml) and stirred at room temperature for 20 h under a nitrogen atmosphere. The reaction mixture was poured into dil. hydrochloric acid (100 ml) containing sodium hydrogensulfite and extracted with chloroform. The chloroform solution was washed with dil. hydrochloric acid (100 ml ×2), brine (100 ml) and dried over anhydrous sodium sulfate, and concentrated. The crude product was chromatographed on silica gel to give 127 mg (87%) of **5**. Recrystallization from hexane–ethanol (5:1) gave an analytical sample, mp 131—132 °C. IR (KBr) 3100—2500 (broad, OH), 1695, 1670 (each C=O), 1610, 1585, 1265 (C–O), and 1070 cm^{-1}; ^{1}H NMR δ=3.91, 3.94, 3.98, 3.99 (each s, 3H, OCH_3), 6.99 (s, 2H, 2×ArH), 7.46 (s, 1H, ArH), and 11.23 (broad, 1H, COOH); ^{13}C NMR δ=56.70, 56.87, 57.90, 64.41 (each OCH_3), 106.36 (C-3), 108.94 (C-7), 111.85 (C-6), 118.37, 121.17, 123.28, 150.49 (C-5), 150.83 (C-4), 151.46 (C-8), 153.92 (C-1), and 165.81 (COOH); MS, m/z 292 (M^+), 277, 259, 247. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52%. Found: C, 61.36; H, 5.45%.

2-Cyano-1,4,5,8-tetramethoxynaphthalene (6). A solution of chlorosulfonyl isocyanate (700 mg, 4.4 mmol) in dichloromethane (2 ml) was added to a solution of 1,4,5,8-tetramethoxynaphthalene(**1**)[2] (992 mg, 4 mmol) in dichloromethane (28 ml) and stirred at room temperature for 2 h. *N,N*-Dimethylformamide (800 mg) was added and stirred at room temperature for 3.5 h. The reaction mixture was poured into ice water and extracted with dichloromethane (100 ml×3). The dichloromethane solution was washed with brine (100 ml) and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica-gel chromatography to give 778 mg (71%) of **6**. Recrystallization from hexane gave an analytical sample, mp 127—128 °C. IR (KBr) 2225 (CN), 1605, 1390, 1370, 1270, 1080, and 1050 cm^{-1}; ^{1}H NMR δ=3.89, 3.94 (each s, 3H, OCH_3), 3.95 (s, 6H, 2×OCH_3), 6.82 (s, 1H, ArH), and 6.97 (s, 2H, 2×ArH); ^{13}C NMR δ=57.04, 57.15, 58.01, 63.56 (each OCH_3), 104.02 (C-2), 106.71 (C-3), 109.28 (C-7), 112.19 (C-6), 117.11, 122.34, 122.71, 150.72 (C-5), 151.35 (C-8), 153.69 (C-4), 155.46 (C-1); MS, m/z 273 (M^+), 258, 243, 215. Calcd for $C_{15}H_{15}O_4N$: C, 65.93; H, 5.53; N, 5.13%. Found: C, 65.85; H, 5.61; N, 5.07%.

2-Bromo-1,4,5,8-tetramethoxynaphthalene (7) and 2,6-Dibromo-1,4,5,8-tetramethoxynaphthalene (8). A solution of bromine (323 mg, 2.02 mmol) in chloroform (5 ml) was added dropwise to a solution of 1,4,5,8-tetramethoxynaphthalene (500 mg, 2.02 mmol) in chloroform (20 ml) at room temperature. The solution was stirred for 2 h, poured into water, and extracted with chloroform. The chloroform solution was washed with aqueous sodium hydrogensulfite, sodium hydrogencarbonate and brine and dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel to give 291 mg (44%) of **7**, 140 mg (17%) of **8** and 14 mg (3%) of the starting material **1**.

7: mp 104—105 °C (from hexane); IR(KBr) 1605, 1580, 1380, 1365, 1310, 1260, 1070, and 1040 cm^{-1}; ^{1}H NMR δ=3.82, 3.88 (each s, 3H, OCH_3), 3.92 (each s, 6H, 2×OCH_3), 6.86 (s, 2H, 2×ArH), and 7.00 (each s, 1H, ArH); MS, m/z 328 (M^++2, 99%), 326 (M^+, 100), 313, 311, 232, 217, 204. Calcd for $C_{14}H_{15}O_4Br$: C, 51.40; H, 4.62%. Found: C, 51.27; H, 4.55%.

8: mp 215—216 °C (from methanol); IR (KBr) 1570, 1355, 1310, 1240, 1070, 1030, and 795 cm^{-1}; ^{1}H NMR δ=3.80 (s, 6H, 2×OCH_3), 3.95 (s, 6H, 2×OCH_3), 7.04 (s, 2H, 2×ArH); MS, m/z 408 (M^++4, 51%), 406 (M^++2, 100), 404 (M^+, 50), 391, 312, and 310. Calcd for $C_{14}H_{14}O_4Br_2$: C, 41.41; H, 3.47%. Found: C, 41.00; H, 3.46%.

2,6-Dibromo-5,8-dihydroxy-1,4-naphthoquinone (10). To a solution of the tetramethoxydibromide **8** (200 mg, 0.49 mmol) in dichloromethane (15 ml) was added dropwise boron tribromide (500 mg, 1.96 mmol) in dichloromethane (5 ml) at −70 °C. After stirring at −70 °C for 4 h, the solution was allowed to warm to room temperature and to stand overnight. It was then decomposed with dil. hydrochloric acid (100 ml) and extracted with dichloromethane (100 ml×3). The dichloromethane solution was worked up as usual and gave a crude product which was chromatographed on a silica-gel column to give 156 mg (91%) of **10**. Recrystallization from ethanol gave an analytical sample, mp 258—261 °C (decomp). IR (KBr) 1610 (C=O), 1580, 1560, 1420, 1400, 1260, 1180, and 995 cm^{-1}; ^{1}H NMR δ=7.61 (s, 2H, 2×ArH) and 12.56 (s, 2H, 2×OH); MS, m/z 350 (M^++4, 51%), 348 (M^++2, 100), 346 (M^+, 52), 304, 302, 269, and 267. Calcd for $C_{10}H_4O_4Br_2$: C, 34.52; H, 1.16%. Found: C, 34.40; H, 1.28%.

2-Acetoxy-1,4,5,8-tetramethoxynaphthalene (12) and 5,8-Dimethoxy-1,4-naphthoquinone (13). Lead tetraacetate (244 mg, 0.55 mmol) was added to a solution of the tetramethoxynaphthalene **1** (124 mg, 0.5 mmol) in benzene (20 ml) and stirred at 60 °C for 1 h. It was then decomposed by the addition of water and extracted with dichloromethane. The usual work-up and chromatography on silica gel gave 62 mg (40%) of **12** and 60 mg (46%) of **13**.

12: mp 85—85.5 °C (from hexane); IR (KBr) 1760 (C=O), 1600, 1365, 1265, 1205, 1090, 1065, 1025, and 990 cm^{-1}; ^{1}H NMR δ=2.37 (s, 3H, $COCH_3$), 3.78, 3.88 (each s, 3H, OCH_3), 3.91 (s, 6H, 2×OCH_3), 6.64 (s, 1H, ArH), and 6.82 (s, 2H, 2×ArH). Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92%. Found: C, 62.73; H, 5.89%.

13: mp 157—159 °C (lit,[3] mp 160—161 °C). This did not depress the melting point of an authentic sample of **13** on admixture.

1,4,5,8-Tetramethoxy-2-naphthol (14). Aqueous sodium hydroxide (1 M, 6 ml; 1 M=1 mol dm^{-3}) was added to a solution of the ester **12** (343 mg, 1.12 mmol) in methanol (8 ml) under a nitrogen atmosphere and stirred at room temperature for 3 h. The solution was acidified by the addition of 1 M hydrochloric acid (100 ml) and extracted with chloroform. The chloroform solution was concentrated to give 269 mg (91%) of **14**, mp 149—152 °C. This was unstable and decomposed during usual recrystallization or column chromatography. IR (KBr) 3400 (sharp OH), 1600, 1375, 1260, 1070 cm^{-1}; ^{1}H NMR δ=3.81, 3.88 (each s, 3H, OCH$_3$), 3.92 (s, 6H, 2XOCH$_3$), 5.20 (broad, 1H, OH), 6.69 (s, 2H, 2XArH), 6.74 (s, 1H, ArH); MS, *m/z* 264 (M$^+$), 249, 221, 203, and 104. HRMS, Calcd for $C_{14}H_{16}O_5$: M, 264.0997. Found: *m/z* 264.0989.

1,2,4,5,8-Pentamethoxynaphthalene (15). Under a nitrogen atmosphere aqueous sodium hydroxide (1 M, 4 ml) was added to a solution of the naphthol **14** (223 mg, 0.84 mmol) in methanol (20 ml) at room temperature. To this solution was altenately added dropwise dimethyl sulfate (1.2 g, 8.4 mmol) and aqueous sodium hydroxide (1 M, 4 ml) at room temperature. After stirring at 50 °C for 2 h, the solution was concentrated until 10 ml and then extracted with chloroform, dried, and concentrated. The residue was chromatographed on silica-gel column to give 141 mg (60%) of **15**. Recrystallization from hexane afforded an analytical sample, mp 104—105 °C. IR (KBr) 1600, 1390, 1370, 1355, 1265, 1070, 1045, and 805 cm^{-1}; ^{1}H NMR δ=3.82 (s, 3H, OCH$_3$), 3.90 (s, 6H, 2XOCH$_3$), 3.94 (s, 3H, OCH$_3$), 3.99 (s, 3H, OCH$_3$), 6.64 (s, 1H, ArH), 6.74 (s, 2H, 2XArH); MS, *m/z* 274 (M$^+$), 264, 263, 249, 231, and 124. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%. Found: C, 64.26; H, 6.74%.

References

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6) The reaction mechanism of aromatic compounds with chlorosulfonyl isocynate was shown in the following paper. G. Lohaus, *Chem. Ber.*, **100**, 2719 (1967).

7) R. E. Moore and P. J. Scheuer, *J. Org. Chem.* **31**, 3272 (1966). For example, in ^{1}H NMR of 2,7-dimethoxynaphthazarin (**A**), two hydroxyl signals were observed at δ 12.70 and 13.12 (Chart 2).

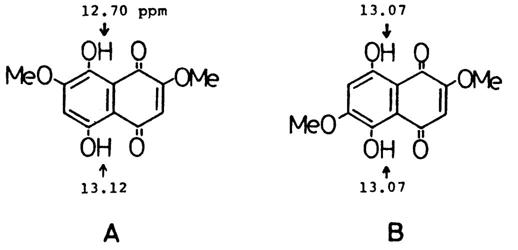

Chart 2.