The Acetylation of Naphthoquinones. The Synthesis of 3-Acetyl-5-methoxy- and 3-Acetyl-5,7-dimethoxy-1,4-naphthoquinones

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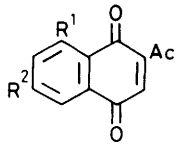
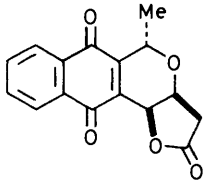
The conversion of 5-methoxy- and 5,7-dimethoxy-1,4-naphthoquinones into their 3-acetyl derivatives is described. A key step is the Fries rearrangement of 1,5-dimethoxy-4-acetoxynaphthalenes to the corresponding 3-acetyl-4-naphthols with boron trifluoride–diethyl ether. Alternative Fries rearrangement of 1-acetoxy-4-hydroxy-5-methoxynaphthalenes gave the 3-acetylquinols, involving *meta* migration of the acetyl group. A convenient new synthesis of 2-acetyl-1,4-naphthoquinone is also reported.

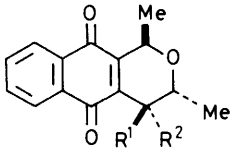
The naphtho[2,3-*c*]pyran ring system occurs not infrequently in Nature as derivatives of the 5,10-quinone. Examples are the eleutherins,[1] the nanaomycins,[2] and the protoaphins.[3] Certain analogues lacking oxygen(s) in the aromatic ring have been synthesised using 2-acetyl-1,4-naphthoquinone (**1**) as starting material; for example, 9-deoxykalafungin (**4**)[4] and 7,9-dideoxyquinones A (**5**) and A′ (**6**),[5] the latter being derivatives of the protoaphins. Preparation of the natural products themselves requires appropriate regiospecific aromatic oxygenation of 2-acetylnaphthoquinone. We describe here syntheses of 3-acetyl-5-methoxy-1,4-naphthoquinone (**2**) † and the corresponding 5,7-dimethoxy analogue (**3**),[7] and are currently investigating the use of these in the formation of several naturally occurring quinones or their derivatives. In the course of this work, an unusual Fries rearrangement was established.



(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = OMe$, $R^2 = H$
(**3**) $R^1 = R^2 = OMe$



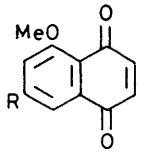
(**4**)



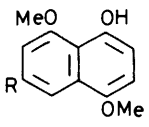
(**5**) $R^1 = OH$, $R^2 = H$
(**6**) $R^1 = H$, $R^2 = OH$

Results and Discussion

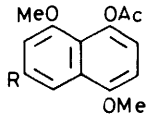
Juglone methyl ether (**7**) was reductively monomethylated at the less hindered oxygen to give the naphthol (**9**)[8] using sodium dithionite followed by treatment with dimethyl sulphate and potassium carbonate in acetone. The corresponding acetate (**11**) was treated with boron trifluoride–diethyl ether at 60 °C for 30 min to give the product (**13**) of Fries rearrangement, together with deacylated material (**9**) which could be recycled, thereby providing a high yield of (**13**). The assignment of structure (**13**) to the product was supported *inter alia* by a sharp lowfield singlet at δ 13.46 in its ^{1}H n.m.r. spectrum due to the strongly hydrogen bonded hydroxy group. Oxidation of this compound with ceric ammonium nitrate gave rise to the desired 3-acetyl-5-methoxy-1,4-naphthoquinone (**2**) in an overall yield of 67% from (**7**).



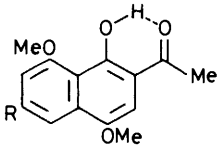
(**7**) R = H
(**8**) R = OMe



(**9**) R = H
(**10**) R = OMe



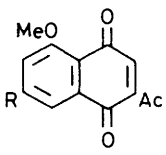
(**11**) R = H
(**12**) R = OMe



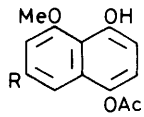
(**13**) R = H
(**14**) R = OMe

5,7-Dimethoxy-1,4-naphthoquinone (**8**) could be converted similarly into its 3-acetyl derivative (**3**) *via* the sequence (**8**) ⟶ (**10**) ⟶ (**12**) ⟶ (**14**) ⟶ (**3**). Assignment of structure (**10**) to the product of reductive monomethylation of (**8**) rested on a comparison with the conversion of (**7**) into (**9**) and also the appearance of a sharp, lowfield, concentration-independent singlet at δ 8.72 for the hydrogen-bonded hydrogen [the corresponding signal for (**9**) occurred at δ 8.92].

The possibility was investigated of synthesising 2-acetyl-5-methoxy-1,4-naphthoquinone (**15**) and its 7-methoxy analogue (**16**), isomeric with (**2**) and (**3**) respectively. Reductive acetylation of the quinone (**7**) with zinc, acetic anhydride, and pyridine in boiling chloroform provided the monoacetate (**17**),



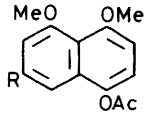
(**15**) R = H
(**16**) R = OMe



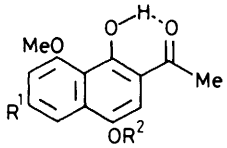
(**17**) R = H
(**18**) R = OMe

† Compound (**2**) is already known.[6] However the yield (34%) in the final step made an alternative route desirable for further synthesis.

acetylation having occurred at the less hindered oxygen. The assignment was supported by a lowfield singlet at δ 9.25, and confirmed by methylation of (**17**) to (**19**), which proved to be isomeric with compound (**11**). Treatment of (**17**) with boron trifluoride–diethyl ether at 60 °C resulted in the formation of 3-acetyl-5-methoxynaphthoquinol (**21**), in which rearrangement the acetyl had undergone *meta* migration, together with deacetylated material. Acetylation of the reaction mixture converted the latter into starting material (**17**) for recycling, while (**21**) was converted into its monoacetate (**22**). Oxidation of (**22**) with ceric ammonium nitrate furnished quinone (**2**), rather than the isomeric (**15**), which confirmed the *meta*-migration of acetyl in the conversion of (**17**) into (**21**). Further proof was acquired by reductive acetylation of the quinone (**2**) derived from the naphthol (**13**) into a monoacetate identical with (**22**).



(**19**) R = H
(**20**) R = OMe



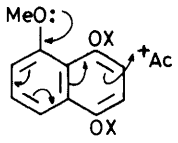
(**21**) $R^1 = R^2 = H$
(**22**) $R^1 = H$, $R^2 = Ac$
(**23**) $R^1 = OMe$, $R^2 = H$
(**24**) $R^1 = OMe$, $R^2 = Ac$

Omission of the acetylation step (**21**) to (**22**) gave poor overall yields of the quinone (**2**) from the acetate (**17**), owing to difficulties in handling the quinol (**21**).

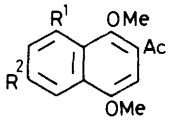
The quinonoid dimethyl ether (**8**) was similarly reductively monacetylated to (**18**), whose structure was confirmed by methylation to (**20**), isomeric with (**12**). Compound (**18**) also underwent *meta*-migration of acetyl with boron trifluoride–diethyl ether to afford (**23**), together with deacylated material. The reaction mixture was monoacetylated as before to yield (**18**) and (**24**), and the latter gave the quinone (**3**) on ceric ammonium nitrate oxidation. Reductive monoacetylation of (**3**) derived *via* (**14**) gave rise to (**24**), to further confirm the *meta*-migration.

The mechanism of the Fries rearrangement is regarded as either intra- or inter-molecular,[9] and commonly the latter, at least in part. This being so, the unusual *meta*-product observed here presumably arises through intermolecular migration of the acylium ion to C-3, this being the position most activated to electrophilic attack, as in (**25**).

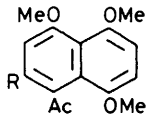
Other routes to acetylated naphthoquinones were also investigated. 1,4-Dimethoxynaphthalene was acetylated with acetic acid in trifluoroacetic anhydride[10] to give the 2-acetyl derivative (**26**) in good yield. This was smoothly oxidatively demethylated to the quinone (**1**) with silver(II) oxide; the alternative oxidant ceric ammonium nitrate proved much less effective in this instance. It might be reasoned that similar acetylation of 1,4,5-trimethoxynaphthalene would afford the 3-acetyl derivative (**27**) since reaction might be expected in the dioxygenated ring, and any influence the 5-methoxy group might have on substitution in the alternative ring might be expected to favour electrophilic attack at C-3. However, reaction with acetic acid and trifluoroacetic anhydride effected monoacylation in the less substituted ring at C-8 to give (**29**), as judged by the ^1H n.m.r. spectrum of the product, in which the signals due to the three adjacent aromatic protons in the starting material had been replaced by a pair of *ortho*-coupled doublets. Assignment of structure (**29**) to the product was preferred to the 6-acetyl isomer since the chemical shifts of these protons were similar to those of 6-H and 7-H in the starting material.



(**25**) X = H or BF_3^-



(**26**) $R^1 = R^2 = H$
(**27**) $R^1 = OMe$, $R^2 = H$
(**28**) $R^1 = R^2 = OMe$



(**29**) R = H
(**30**) R = OMe

1,4,5,7-Tetramethoxynaphthalene is readily prepared by Birch's[11] method, although we made it in high yield by hydrolysis and methylation of the acetate (**20**), since an excess of this material was available. The reaction of 1,4,5,7-tetramethoxynaphthalene with acetic acid and trifluoroacetic anhydride was investigated since the 7-methoxy group might tend to prevent acetylation at C-8 through crowding, and the effect of the C-5 and C-7 methoxy groups should be additive in promoting attack at C-3. This reasoning was partially borne out in practice, two isomeric products being formed cleanly in a ratio of 1:3. The major isomer (**30**) showed an *ortho*-coupled pair of doublets and a highfield one-proton singlet at δ 6.68, while the minor isomer (**28**) showed two *meta*-coupled doublets and a singlet at δ 7.14. The assignment of structure (**28**) rather than the isomeric 2-acetyl compound was confirmed by methylation of the naphthol (**14**), which gave the same product. Compound (**28**) was smoothly oxidised to the quinone (**3**) using silver(II) oxide, which confirmed that this tetramethyl ether could be oxidised successfully.

We are investigating the possibility of modifying the protection of the C-7 oxygen, for example, with a group of larger steric requirement than methyl, in an attempt to achieve specific acylation at C-3.

Experimental

All ^1H n.m.r. spectra were measured for solutions in [^2H]chloroform with tetramethylsilane as internal reference, while i.r. spectra were measured for Nujol mulls. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while column chromatography refers to dry-packed columns using the same gel (70—230 mesh). Light petroleum refers to the fraction of b.p. 60—80 °C. The phrase 'residue obtained upon work-up' refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

1,5-*Dimethoxy*-4-*naphthol* (**9**).—Juglone methyl ether (**7**) (6.34 g) was dissolved in dichloromethane (150 ml) and diethyl ether (200 ml), and shaken with an aqueous solution (200 ml) containing sodium dithionite (30 g) in a separating funnel. The residue obtained upon work-up of the colourless organic phase was immediately dissolved in dry acetone (300 ml), and dry potassium carbonate (12.8 g) and dimethyl sulphate (12.6 ml) were added, and the mixture boiled under nitrogen for 5 h. The cooled reaction mixture was filtered and evaporated. The residue was dissolved in ether and washed with a 25% ammonia solution, followed by water, dilute hydrochloric acid, and finally water. The organic layer was dried and evaporated to give the

product (6.47 g, 94%), m.p. 155.5—156.5 °C (light petroleum) (lit.,[8] 155—156 °C) (Found: C, 70.6; H, 5.8. Calc. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9%); $\nu_{max.}$ 3 420, 1 630, and 1 609 cm^{-1}; δ 3.92 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 6.77 (2 H, s, 2- and 3-H), 6.81 (1 H, d, *J* 8 Hz, 6-H), 7.31 (1 H, t, *J* 8 Hz, 7-H), 7.85 (1 H, d, *J* 8 Hz, 8-H), and 8.92 (1 H, s, OH, D_2O exchangeable).

1,5,7-*Trimethoxy*-4-*naphthol* (**10**).—5,7-Dimethoxy-1,4-naphthoquinone (1.00 g) was treated as above to give a residue which was chromatographed (eluant 15% ethyl acetate–light petroleum) to yield the product (0.87 g, 81%), m.p. 131—132 °C (light petroleum) (Found: C, 66.8; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%); $\nu_{max.}$ 3 390 and 1 620 cm^{-1}; δ 3.92 (6 H, s, OCH_3), 4.01 (3 H, s, OCH_3), 6.51 (1 H, d, *J* 2 Hz, 6-H), 6.62 and 6.76 (1 H each, d, *J* 8 Hz, 2- and 3-H), 7.15 (1 H, d, *J* 2 Hz, 8-H), and 8.72 (1 H, s, OH, D_2O exchangeable).

4-*Acetoxy*-1,5-*dimethoxynaphthalene* (**11**).—Compound (**9**) (3.67 g), acetic anhydride (13 ml), and pyridine (70 ml) were boiled together for 2 h and then thrown onto ice. The white crystalline solid was filtered off, washed with water, and dried to afford the *product* (4.25 g, 96%), m.p. 119—120 °C (light petroleum) (Found: C, 68.3; H, 5.8. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%); $\nu_{max.}$ 1 750 and 1 600 cm^{-1}; δ 2.35 (3 H, s, CCH_3), 3.91 and 3.96 (3 H each, s, OCH_3), 6.74 (1 H, d, *J* 8 Hz, 2-H), 6.87 (1 H, d, *J* 8 Hz, 6-H), 6.96 (1 H, d, *J* 8 Hz, 3-H), 7.37 (1 H, t, *J* 8 Hz, 7-H), and 7.88 (1 H, d, *J* 8 Hz, 8-H).

4-*Acetoxy*-1,5,7-*trimethoxynaphthalene* (**12**).—The naphthol (0.86 g) was treated as above to give the *product* (0.86 g, 85%), m.p. 145—146 °C (ethanol) (Found: C, 65.1; H, 5.8. $C_{15}H_{16}O_5$ requires C, 65.1; H, 5.8%); $\nu_{max.}$ 1 750, 1 630, and 1 610 cm^{-1}; δ 2.33 (3 H, s, CCH_3), 3.88, 3.91, and 3.97 (3 H each, s, OCH_3), 6.54 (1 H, d, *J* 2 Hz, 6-H), 6.73 and 6.85 (1 H each, d, *J* 8 Hz, 2- and 3-H), and 7.19 (1 H, d, *J* 2 Hz, 8-H).

3-*Acetoxy*-1,5-*dimethoxy*-4-*naphthol* (**13**).—The acetate (**11**) (1.39 g) and boron trifluoride (13 ml) were stirred together for 30 min at 60 °C (bath temp.). The reaction mixture was thrown onto ice (20 ml) and extracted with dichloromethane. The residue obtained upon work-up of the organic phase was chromatographed (eluant 5% ethyl acetate in light petroleum). Early fractions afforded compound (**9**) (0.28 g), while later fractions afforded the *product* (0.96 g, 69 or 86% based on unrecovered starting material), as green needles, m.p. 132.5—133.5 °C (light petroleum) (Found: C, 68.0; H, 5.65. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.70%); $\nu_{max.}$ 1 615br and 1 575 cm^{-1}; δ 2.69 (3 H, s, CCH_3), 3.95 and 4.04 (3 H each, s, OCH_3), 6.95 (1 H, d, *J* 8 Hz, 6-H), 6.97 (1 H, s, 2-H), 7.51 (1 H, t, *J* 8 Hz, 7-H), 7.85 (1 H, d, *J* 8 Hz, 8-H), and 13.46 (1 H, s, OH, D_2O exchangeable).

3-*Acetyl*-1,5,7-*trimethoxy*-4-*naphthol* (**14**).—The acetate (**12**) (0.332 g) and boron trifluoride (4 ml) were heated as above. The residue was chromatographed (30% ethyl acetate in light petroleum) to give first the naphthol (**10**) (0.05 g, 19%), followed by the *product* (0.222 g, 67 or 83% based on unrecovered starting material) as yellow-green crystals, m.p. 174—175 °C (ethanol) (Found: C, 64.9; H, 5.9. $C_{15}H_{16}O_5$ requires C, 65.1; H, 5.8%); $\nu_{max.}$ 1 600br cm^{-1}; δ 2.63 (3 H, s, CCH_3), 3.92 (6 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 6.52 (1 H, d, *J* 2 Hz, 6-H), 6.86 (1 H, s, 2-H), 7.10 (1 H, d, *J* 2 Hz, 8-H), and 14.00 (1 H, s, OH, D_2O exchangeable).

3-*Acetyl*-5-*methoxy*-1,4-*naphthoquinone* (**2**).—(a) *From compound* (**13**). A solution of ceric ammonium nitrate (482 mg) in water (3 ml) was added dropwise with stirring over a period of 5 min to a solution of compound (**13**) (100 mg) in acetonitrile (7 ml). The solution was stirred for a further 15 min and then poured into water. This was extracted with dichloromethane, and the residue upon work-up gave the *product* (82 mg, 89%) as yellow needles, m.p. 102—103 °C (dichloromethane–light petroleum) (lit.,[6] 103.5—104.5 °C).

(b) *From compound* (**22**). Ceric ammonium nitrate (362 mg) in water (2 ml) was used to oxidise the acetate (**22**) (85 mg) in acetonitrile (10 ml) as in (a) above. This gave the *product* (63 mg, 91%).

3-*Acetyl*-5,7-*dimethoxy*-1,4-*naphthoquinine* (**3**).—(a) *From compound* (**14**). Compound (**14**) (65 mg) when oxidised as above afforded the *product* (51 mg, 86%) as orange crystals, m.p. 146—149 °C (decomp.) (dichloromethane–light petroleum) (Found: C, 64.3; H, 4.8. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.6%); $\nu_{max.}$ 1 645 and 1 595 cm^{-1}; δ 3.95 and 3.97 (3 H each, s, OCH_3), 6.74 (1 H, d, *J* 2 Hz, 6-H), 6.83 (2 H, s, 2- and 3-H), and 7.24 (1 H, d, *J* 2 Hz, 8-H).

(b) *From compound* (**24**). The acetate (**24**) (116 mg) was oxidised as above to give the product (94 mg, 90%).

(c) *From compound* (**28**). Compound (**28**) (76 mg) in dioxane (5 ml) containing silver(II) oxide (130 mg) was treated with nitric acid (6M; 0.4 ml) and stirred at room temperature for 3.5 min. Work-up as for compound (**1**) below gave the residue which was rapidly chromatographed (eluant 40% ethyl acetate–light petroleum) to give the quinone (52 mg, 77%) identical with the material from (a) and (b) above.

1-*Acetoxy*-5-*methoxy*-4-*naphthol* (**17**).—Juglone methyl ether (**7**) (520 mg) in chloroform (15 ml) was treated with acetic anhydride (0.7 ml), pyridine (0.7 ml), and zinc dust (2 g), and the mixture was gently boiled under nitrogen with vigorous stirring for 15 min. It was cooled, filtered, and the filtrate was poured into water and stirred for 10 min. The organic phase was briefly shaken with water (30 ml) containing concentrated hydrochloric acid (1 ml), followed by water (2 × 30 ml). The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate in light petroleum) to yield the product (468 mg, 72%) as colourless needles, m.p. 82—83 °C (ethyl acetate–light petroleum) (Found: C, 67.2; H, 5.0. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); $\nu_{max.}$ 3 370 and 1 740 cm^{-1}; δ 2.41 (3 H, s, CCH_3), 4.03 (3 H, s, OCH_3), 6.78 (1 H, dd, *J* 6 and 3 Hz, 6-H), 6.81 (1 H, d, *J* 9 Hz, 3-H), 7.12 (1 H, d, *J* 9 Hz, 2-H), 7.3—7.5 (2 H, m, 7- and 8-H), and 9.25 (1 H, s, OH, D_2O exchangeable).

1-*Acetoxy*-5,7-*dimethoxy*-4-*naphthol* (**18**).—The quinone (**8**) (1.00 g) was reductively acetylated as above. Chromatography (eluant 20% ethyl acetate in light petroleum) gave the *product* (0.96 g, 80%) as colourless needles, m.p. 134—135 °C (ethyl acetate–light petroleum) (Found: C, 63.9; H, 5.2. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); $\nu_{max.}$ 3 375 and 1 750 cm^{-1}; δ 2.40 (3 H, s, CCH_3), 3.87 and 3.98 (3 H each, s, OCH_3), 6.46 (1 H, d, *J* 2 Hz, 6-H), 6.63 (1 H, d, *J* 2 Hz, 8-H), 6.68 (1 H, d, *J* 9 Hz, 3-H), 7.08 (1 H, d, *J* 9 Hz, 2-H), and 9.07 (1 H, s, OH, D_2O exchangeable).

1-*Acetoxy*-4,5-*dimethoxynaphthalene* (**19**).—Compound (**17**) (160 mg) in dry acetone (30 ml) was treated with an excess of potassium carbonate (1.6 g) and dimethyl sulphate (1.4 ml) and the mixture boiled with vigorous stirring for 3 h. It was then cooled, filtered, the solvent evaporated, and the residue chromatographed (eluant 15% ethyl acetate in light petroleum) which also removed the excess of dimethyl sulphate. The *product* (135 mg, 79%) was obtained as colourless crystals, m.p. 62 °C (dichloromethane–light petroleum) (Found: C, 68.0; H, 5.7. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%); $\nu_{max.}$ 1 750 cm^{-1}; δ 2.42 (3 H, s, CCH_3), 3.96 (6 H, s, OCH_3), 6.81 (1 H, d, *J* 9 Hz, 3-H), 6.8—7.0 (1 H, m, 6-H), 7.16 (1 H, d, *J* 9 Hz, 2-H), and 7.3—7.5 (2 H, m, 7- and 8-H).

1-*Acetoxy*-4,5,7-*trimethoxynaphthalene* (**20**).—Compound (**18**) (170 mg) was methylated as above, and the reaction mixture chromatographed (eluant 15% ethyl acetate in light petroleum) to yield the *product* (138 mg, 77%) as white cubes, m.p. 110—112 °C (methylene chloride–light petroleum) (Found: C, 65.05; H, 5.85. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%); $\nu_{max.}$ 1 751, 1 640, 1 611, and 1 588 cm^{-1}; δ 2.42 (3 H, s, CCH_3), 3.90 (3 H, s, OCH_3), 3.94 (6 H, s, OCH_3), 6.55 and 6.67 (1 H each, d, *J* Hz, 6- and 8-H), 6.68 (1 H, d, *J* 9 Hz, 3-H), and 7.12 (1 H, d, *J* 9 Hz, 3-H).

1-*Acetoxy*-3-*acetyl*-5-*methoxy*-4-*naphthol* (**22**).—(a) *From compound* (**17**). Compound (**17**) (100 mg) was stirred in boron trifluoride–diethyl ether (1 ml) at 65 °C for 30 min under nitrogen after which the mixture was poured into cold water, stirred for 10 min, and extracted with dichloromethane. The residue obtained upon work-up was dissolved in chloroform (20 ml) and acetic anhydride (0.2 ml), pyridine (0.2 ml), and zinc dust (0.4 g) [to ensure that any quinone present by oxidation of (**21**) was reduced to the hydroquinone level] were added. The mixture was gently boiled with vigorous stirring under nitrogen for 15 min. The reaction mixture was cooled, filtered, and the filtrate poured into water (20 ml) and stirred for 10 min. The organic phase was briefly shaken with water (30 ml) containing concentrated hydrochloric acid (1 ml), separated, and washed with water (2 × 30 ml). The residue obtained upon work-up was chromatographed (25% ethyl acetate in light petroleum) to yield starting material (**17**) (35 mg, 35%) followed by the *product* (43 mg, 36 or 66% based on unrecovered starting material) as yellow needles, m.p. 130—131 °C (methylene chloride–light petroleum) (Found: C, 65.5; H, 5.1. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%); $\nu_{max.}$ 1 750 and 1 620 cm^{-1}; δ 2.44 (3 H, s, $OCOCH_3$), 2.67 (3 H, s, $CCOCH_3$), 4.05 (3 H, s, OCH_3), 6.94 (1 H, d, *J* 8 Hz, 6-H), 7.32 (1 H, d, *J* 8 Hz, 8-H), 7.45 (1 H, s, 2-H), 7.54 (1 H, t, *J* 8 Hz, 7-H), and 14.08 (1 H, s, OH, D_2O exchangeable).

(b) *From compound* (**2**). A mixture of compound (**2**) (75 mg) in chloroform (20 ml) containing acetic anhydride (0.2 ml), pyridine (0.2 ml), and zinc dust (0.4 g) was gently boiled for 15 min with vigorous stirring under nitrogen. The reaction mixture was worked up and chromatographed as for compound (**17**) to give the product (57 mg, 63%), identical with that obtained in (a) above.

1-*Acetoxy*-3-*acetyl*-5,7-*dimethoxy*-4-*naphthol* (**24**).—(a) *From compound* (**18**). Compound (**18**) (100 mg) was treated as in (a) above, and chromatography (same eluant) gave starting material (31 mg, 31%) followed by *product* (59 mg, 51 or 86% based on unrecovered starting material) as light yellow needles, m.p. 183—184 °C (dichloromethane–light petroleum) (Found: C, 63.2; H, 5.3. $C_{16}H_{16}O_6$ requires C, 63.2; H, 5.2%); $\nu_{max.}$ 1 748 and 1 600 cm^{-1}; δ 2.43 (3 H, s, $OCOCH_3$), 2.61 (3 H, s, $CCOCH_3$), 3.90 and 3.99 (3 H, each s, OCH_3), 6.53 and 6.62 (1 H, each d, *J* 2 Hz, 6- and 8-H), 7.40 (1 H, s, 2-H), and 14.46 (1 H, s, OH, D_2O exchangeable).

(b) *From compound* (**3**). Compound (**3**) (50 mg) was reductively monoacetylated as for (**22**) (route b) to yield the *product* (46 mg, 78%), identical with that described above.

2-*Acetyl*-1,4-*dimethoxynaphthalene* (**26**).—1,4-Dimethoxynaphthalene (22 g) was treated with a mixture of acetic acid (7.0 ml) and trifluoroacetic anhydride (26.5 ml), and the flask was heated at 60 °C for 1.5 h. Aqueous sodium hydroxide (2.5M) was added to the cooled reaction mixture until it became alkaline. Extraction with dichloromethane and work-up of the organic phase gave a dark crystalline mass which was sublimed (105 °C/1 mmHg) to afford the *product* (21.5 g, 80%), m.p. 61—62 °C (light petroleum) (lit.,[12] 59—60.5 °C).

2-*Acetyl*-1,4-*naphthoquinone* (**1**).—Compound (**26**) (4.46 g) in dioxane (220 ml) containing silver(II) oxide (9.62 g) was treated dropwise with nitric acid (6M; 19.4 ml). The reaction was vigorously stirred until the oxidant was consumed (*ca.* 2 min) and then quenched by the addition of dichloromethane–water (4:1; 200 ml). After washing with water, the organic phase was worked up to give the quinone in virtually quantitative yield, and identical with authentic material. The product was used as such without further purification in subsequent reactions.[13]

8-*Acetyl*-1,4,5-*trimethoxynaphthalene* (**29**).—A mixture of trifluoroacetic anhydride (0.28 ml) and acetic acid (0.11 ml) was added to 1,4,5-trimethoxynaphthalene (0.40 g) in dry methylene chloride at 0 °C. The solution was stirred for 2 h and then added to an excess of 10% aqueous sodium hydrogen carbonate, which was then extracted with methylene chloride. Work-up of the organic layer afforded a residue which was chromatographed (10% ethyl acetate in light petroleum) to give starting material (0.13 g), followed by the *product* (0.255 g, 79% based on unrecovered starting material), m.p. 116—117 °C (ethanol) (Found: C, 69.2; H, 6.3. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.15%); $\nu_{max.}$ 1 670 and 1 585 cm^{-1}; δ 2.44 (3 H, s, CCH_3), 3.84, 3.92, and 3.97 (3 H each, s, OCH_3), 6.84 (1 H, d, *J* 8 Hz, 6-H), 6.85 (2 H, s, 2- and 3-H), and 7.21 (1 H, d, *J* 8 Hz, 7-H). For 1,4,5-trimethoxynaphthalene, the resonances for 6-H, 7-H, and 8-H are δ 6.90, 7.38, and 7.86, respectively.

1,4,5,7-*Tetramethoxynaphthalene*.—The acetate (**20**) (148 mg) in ethanol (20 ml) was alternately treated with portions of potassium hydroxide (300 mg) in water (1 ml) and dimethyl sulphate (0.51 ml). The resulting solution was heated at 90 °C (bath) for 2.5 h. The solvent was removed from the cooled solution, and the residue partitioned between water and dichloromethane. The contents of the organic layer on work-up were chromatographed (eluant 30% ethyl acetate in light petroleum) to give the product (135 mg, virtually quantitative) which was recrystallised from light petroleum to give white cubes, m.p. 115—116 °C (lit.,[11] 131—132 °C) (Found: C, 67.55; H, 6.55. $C_{14}H_{16}O_4$ requires C, 67.75; H, 6.45%); $\nu_{max.}$ 1 623 and 1 597 cm^{-1}; δ 3.90 and 3.92 (3 H each, s, OCH_3), 3.95 (6 H, s, OCH_3), 6.57 (1 H, d, *J* 2 Hz, 6-H), 6.63 and 6.74 (1 H, each d, *J* 8 Hz, 2- and 3-H), and 7.09 (1 H, d, *J* 2 Hz, 8-H).

3-*Acetyl*-1,4,5,7-*tetramethoxynaphthalene* (**28**) *and* 8-*Acetyl*-1,4,5,7-*tetramethoxynaphthalene* (**30**).—1,4,5,7-Tetramethoxynaphthalene (80 mg) in dichloromethane (2 ml) was treated at 0 °C with a mixture of trifluoroacetic anhydride (68 mg) and acetic acid (19 mg). The reaction mixture rapidly turned dark grey and was monitored by t.l.c. After 1 h at room temperature, no reaction was apparent, and so a further quantity of the acetylating mixture equal to the above was added. The whole was stirred for a further 20 h. Since some starting material was still present, a further quantity of reagents was added and the reaction stirred for 5 h. The mixture was thrown into aqueous sodium hydrogen carbonate and extracted with dichloromethane. The residue upon work-up was chromatographed (p.l.c. eluant 20% ethyl acetate in light petroleum) to afford starting material (11 mg, 14%) as the front band, followed by 3-*acetyl*-1,4,5,7-*tetramethoxynaphthalene* (**28**) (18 mg, 22% based on unrecovered starting material) as white cubes, m.p. 109—110 °C (light petroleum) (Found: C, 66.25; H, 6.3. $C_{18}H_{18}O_5$ requires C, 66.2; H, 6.2%); $\nu_{max.}$ 1 650, 1 610, and 1 579 cm^{-1}; δ 2.76 (3 H, s, CCH_3), 3.81 and 3.95 (3 H each, s, OCH_3), 4.01 (6 H, s, OCH_3), 6.62 (1 H, d, *J* 2 Hz, 6-H), 7.13 (1 H, s, 2-H), and 7.20 (1 H, d, *J* 2 Hz, 8-H). The band of lowest R_F afforded 8-acetyl-1,4,5,7-tetramethoxynaphthalene (**30**) (53 mg, 66% based on unrecovered starting material), m.p. 152—153 °C

(ethanol) (Found: C, 66.2; H, 6.3. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.2%); $\nu_{max.}$ 1 690 and 1 592 cm^{-1}; δ 2.52 (3 H, s, CCH_3), 3.78 and 3.97 (3 H each, s, OCH_3), 3.89 (6 H, s, OCH_3), 6.62 and 6.76 (1 H each, d, *J* 8 Hz, 2- and 3-H), and 6.68 (1 H, s, 6-H).

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